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Original Communications

THE COLD PRESSOR TEST FOR MEASURING THE REACTIBILITY OF THE BLOOD PRESSURE: DATA CONCERNING 571 NORMAL AND HYPERTENSIVE SUBJECTS*

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THE reactivity of the blood pressure is an index of vasomotor tonus. Studies by many workers have demonstrated that the systemic blood pressure is variable and reacts to many forms of stimulation.^{1, 2, 3} A detailed study of this variability is time consuming and involves numerous estimations of blood pressure in short intervals of time. Many procedures have been tried by us and others; none has had certain or consistent pressor effects on the blood pressure. In 1932 we reported a simple procedure carried out by immersing the extremity in ice water. Measured cold, applied locally, produces a strong, thermosensory stimulus with vasopressor effects in 99 per cent of all subjects. Repetition of the test daily for a period of time shows a remarkable constancy in the response of the blood pressure. As far as known, the response of the blood pressure is characteristic for the individual and probably remains so throughout life. Confirmation of the specificity of the cold pressor test has been given by Briggs and Oerting,⁴ who studied the reaction of 124 normal and hypertensive subjects. Dickman and Michel⁵ have presented similar confirmation as a result of the study of the reaction of a group of pregnant and nonpregnant women.

TECHNIC OF THE COLD PRESSOR TEST

The subject is allowed to rest in a supine position in a quiet room for from twenty to sixty minutes. Several readings of the blood pressure are taken until a basal level has been approximated. The cuff of the sphygmomanometer is placed on one arm of the subject, and the opposite hand is placed in ice water (4° C.) to a point just above the wrist. Readings of the blood pressure are taken at the end of thirty seconds and

*From the Division of Medicine, The Mayo Clinic, Rochester, Minn.

again at the end of sixty seconds. The maximal reading obtained while the hand is in the ice water is taken as the index of the response. The hand is removed from the ice water, and readings are taken every two minutes until the blood pressure returns to its previous basal level. The maximal response usually occurs within thirty seconds. The blood pressure of subjects with normal levels of blood pressure returns to the basal level within two minutes. In the presence of established hypertension, there frequently is a delay in return of the blood pressure to the previous level. Subjects vary greatly in their sensitivity to ice water; for a few, the time of immersion is limited by the pain caused by the cold. There is no relationship between the degree of sensitivity and the response of the blood pressure. No untoward effects have occurred among hypertensive subjects, although increases in blood pressure to the capacity of the sphygmomanometer are occasionally noted.

Two values seem of significance in the cold pressor reaction: first, the increase in the blood pressure from basal to maximal points, which we have designated as the "response or range"; and second, the maximal values obtained in the systolic and diastolic pressures, which we have designated as the "ceiling" for the cold test stimulus. This ceiling is held for a variable time after application of the test. Which of these values is more useful is not known as yet. There is a certain error in the "range" as basal levels may be difficult to obtain.

MECHANISM OF THE REACTION

The most probable explanation of the cause of the rise of blood pressure in the cold pressor test is that the response is a widespread vasopressor reaction initiated through a neurogenic reflex arc. There is no significant change in cardiac rate or in cardiac output during the test. The speed of the reaction and the fact that the reaction is present in completely adrenalectomized dogs and in human beings who have Addison's disease are proof that epinephrine is not the primary factor in producing the reaction. The possibility of a local hormonal substance being generated in the immersed hand as a result of the direct action of the cold is unlikely, as the reaction is not inhibited by a tourniquet placed around the arm so as to shut off the circulation.

CONSTANCY OF THE REACTION

The test has been repeated one or more times after intervals of from three months to three years on twenty-five subjects whose blood pressures were normal and on twenty subjects who had essential hypertension. Four subjects whose blood pressures were normal were subjected to the test at the same time of day, three times a week for four weeks. Two subjects whose blood pressures were normal were subjected to the test twice a day for two weeks. One woman whose blood pressure was normal but who showed an abnormal range and abnormal maximal re-

sponse was subjected to the test fifty-six times in two years. There was an average variation in range of response of only 10 per cent in the group of patients who were subjected to repeated tests. In no case did a subject with a range of less than 18 mm. of mercury in systolic and diastolic pressures give a subsequent reaction in the abnormal range, and in no case did a subject who revealed an abnormal range give a normal reaction. Several subjects who gave reactions in the maximal range of normal on repeated tests gave occasional reactions in the minimal range of the abnormal. This type of subject we have placed in an indeterminate group. We have insufficient data to say what the possible effects of seasonal variations on this reaction are. Subjects with hypertension always give a reaction which is abnormal in maximal response, but repeated tests in months or years may show an increase in range and in maximal response, which correlates with increases in the clinical severity of the hypertension.

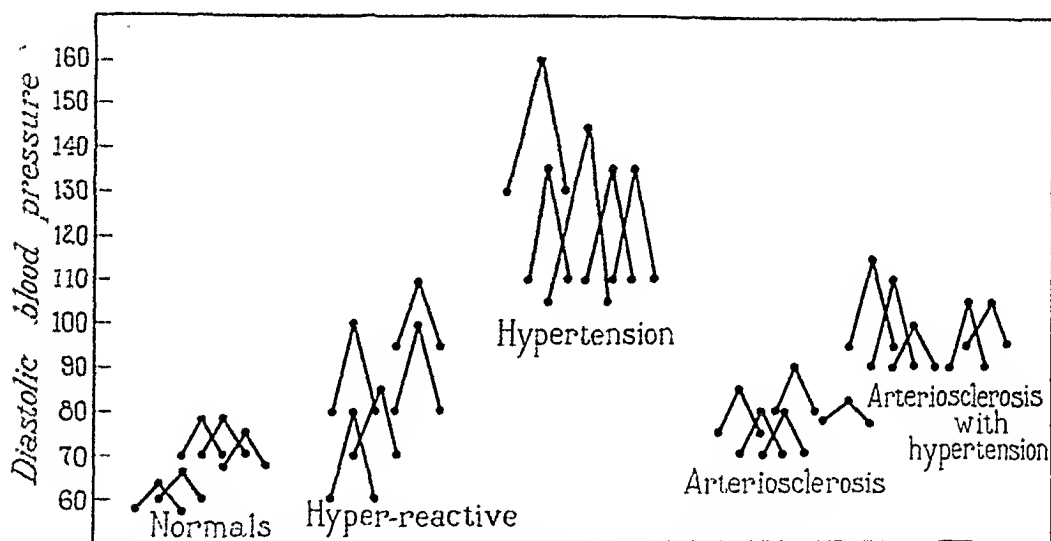


Fig. 1.—Response of blood pressure to cold pressor test.

THE EFFECT OF AGE ON THE REACTION

In the group in which there were normal levels of blood pressure and normal reactions, there was no significant change in the range of the reaction with increasing age (Table I). In the entire group with normal levels of blood pressure, there is a definite increase in the range of the reaction in the latter decades of life. This may be interpreted as indicating that an abnormal hypertonicity of the vasomotor system may increase in intensity with increasing years of life.

Data

We have made two previous preliminary reports on the results obtained with this test.⁶ The present report is based on an observation extending over a period of three years and the application of the test to 571 subjects. The test has been repeated a varying number of times on a number

TABLE I
EFFECT OF AGE ON THE RESPONSE TO COLD PRESSOR TEST

AGE IN YEARS	NORMAL BLOOD PRESSURE AND NORMAL REACTIONS			NORMAL BLOOD PRESSURE (ENTIRE GROUP)		
	NUMBER	SYSTOLIC MM. OF MERCURY	DIASTOLIC MM. OF MERCURY	NUMBER	SYSTOLIC MM. OF MERCURY	DIASTOLIC MM. OF MERCURY
0 to 20	71	11.3 ± 0.84	9.4 ± 0.65	89	12.4 ± 0.91	12.3 ± 0.84
20 to 40	153	10.7 ± 0.93	9.5 ± 0.74	201	12.9 ± 0.87	11.8 ± 0.82
40 or more	64	11.6 ± 0.76	9.9 ± 0.68	98	19.6 ± 1.8	18.4 ± 1.6

of subjects. The entire group can be divided into three categories (Fig. 1). Group 1 includes subjects with normal levels of blood pressure and minimal or normal reactions of the blood pressure to the cold test. These individuals are designated as "normal reactors." They include normal persons and subjects suffering from a variety of diseases not associated with hypertension. Group 2 includes subjects with normal levels of blood pressure who react excessively to the cold test. These individuals we have designated "normal hyperreactors." Group 3 includes subjects with increased levels of blood pressure and other evidences of essential hypertension. A summary of the data in the three groups is shown in Table II.

TABLE II
SUMMARY OF DATA IN COLD TEST

SUBJECTS			MEAN RISE IN BLOOD PRESSURE	
			SYSTOLIC MM. OF MERCURY	DIASTOLIC MM. OF MERCURY
Normal blood pressure	288	4 to 86	11.4 ± 0.9	10.6 ± 0.9
Hyporeactors (0 to 22 mm. of mercury)				
Hyperreactors (22+ mm. of mercury)	90	4 to 75	29.4 ± 4.2	24.5 ± 2.6
Hypertension				
Organic	127	24 to 64	47.2 ± 10.5	34.3 ± 7.9
Preorganic	66	25 to 62	34.4 ± 7.7	25.4 ± 4.5

Group 1, Normal Subjects.—In this group are those subjects with normal blood pressure and with minimal increase in blood pressure. The mean increase in this group was 11.4 mm. of mercury for the systolic and 10.6 mm. of mercury for the diastolic pressure. The values were from 0 to 22 mm. of mercury. The latter was tentatively placed as the upper limit of the normal response. In 96 per cent of those cases in which there was a normal or minimal response, the rise in systolic and diastolic blood pressure was less than 15 mm. of mercury.

Group 2, Normal Hyperreactors.—This group comprises ninety subjects of both sexes. Many normal hyperreactors were found in the course of general examination at the clinic. The readings of the blood pressure,

when taken under usual conditions, always were in the range of the normal. The ages of these subjects varied from four to seventy-five years. The value for the mean rise in blood pressure with the cold pressor test was 29.4 mm. of mercury for the systolic and 24.5 mm. of mercury for the diastolic pressure. This group is of great significance, and the crucial question is, do these subjects represent potential hypertension? Complete proof of this assumption is not at hand, but there is some evidence that such is the case. A careful investigation of the family history of these subjects, as related to possible incidence of hypertension, discloses that of these ninety subjects who revealed a hyperreaction, seventy-eight had a positive family history of hypertensive cardiovascular disease. If this is compared to the family history of hypertensive cardiovascular disease among 14 per cent of the group of subjects with normal reactions, the significance of the hyperreaction in "normal subjects" becomes more impressive. There is some additional proof accumulating. Of the original group of eight "hyperreactor normals" reported in 1932, three have developed clinical degrees of essential hypertension with elevation of the blood pressure and demonstrable hypertensive changes in the retinal arterioles. Brief protocols of the three cases are as follows:

CASE 1.—A woman was admitted to the clinic seven times in all. Previous to the time the cold pressor test was devised, her relevant history was as follows: On her examination in 1925 she was thirty years old and had bronchiectasis. Her blood pressures, in millimeters of mercury, were 138 systolic and 74 diastolic. On a second admission in 1926, she had exophthalmic goiter, and a thyroidectomy was performed; her blood pressures, systolic and diastolic, taken at different times, were 126 and 80, 116 and 74, and 134 and 74. She was admitted the third time in 1928; the systolic pressure ranged from 124 to 132 and the diastolic from 82 to 84. In 1930, the blood pressures were 118 systolic and 80 diastolic. The fifth registration was in 1932, when the systolic pressure ranged from 116 to 120 and the diastolic from 65 to 75. With the cold pressor test, the blood pressures were increased from a basal level of 125 for the systolic and 80 for the diastolic to 165 for the systolic and 115 for the diastolic. Examination of the ocular fundi did not reveal anything abnormal. Inquiry concerning her family revealed that her mother, aged sixty-three years, had high blood pressure and that her father, aged sixty-five years, had high blood pressure and recently had had a coronary occlusion. A diagnosis was made of a prehypertensive state. On her sixth registration at the clinic, in October, 1933, daily readings of the blood pressure varied from 100 to 132 systolic and from 58 to 88 diastolic. The response to the cold pressor test was from a basal level of 120 for the systolic pressure and 75 for the diastolic to 165 for the systolic pressure and 110 for the diastolic. Examination of the ocular fundi revealed very slight narrowing of the retinal arterioles. The basal metabolic rate was -4 per cent. On her seventh visit to the clinic, in January, 1935, daily readings of blood pressure revealed a variation of from 150 to 155 systolic and from 100 to 105 diastolic. The response to the cold pressor test was from a basal level of 130 for the systolic pressure and 80 for the diastolic to a maximum of 175 for the systolic pressure and 120 for the diastolic. Examination of the ocular fundi disclosed narrowing of the retinal arteries, grade 2. The basal metabolic rate was -3 per cent. The diagnosis was essential hypertension in the preorganic stage.

CASE 2.—A man was forty-two years old on his first registration at the clinic in March, 1931. Many daily readings revealed a variation of from 126 to 140 mm. of mercury for the systolic and from 50 to 90 for the diastolic. Examination of the ocular fundi did not reveal anything abnormal. The response to the cold pressor test was from a basal level of 120 for the systolic pressure and 55 for the diastolic to a maximum of 150 for the systolic pressure and 100 for the diastolic. The diagnosis was thromboangiitis obliterans and a prehypertensive state. On his second visit to the clinic, in January, 1934, many daily readings of the blood pressure revealed a variation of from 108 to 140 systolic and from 65 to 85 diastolic. Examination of the ocular fundi disclosed some narrowing of the retinal arterioles. The diagnosis was the same as it had been at his previous visit to the clinic. On his third registration in January, 1935, the readings for the blood pressure, which were taken in the office, were 184 systolic and 110 diastolic, and 158 systolic and 95 diastolic. Hourly readings of the blood pressure, while the patient was resting, revealed a variation of from 140 to 165 for the systolic pressure and a variation of from 90 to 105 for the diastolic. The response of the blood pressure to the cold pressor test was from a basal level of 130 for the systolic and 80 for the diastolic to a maximum of 175 for the systolic and 110 for the diastolic. Examination of the ocular fundi revealed narrowing of the retinal arteries, grade 2, and sclerosis of the hypertensive type, grade 1. The diagnosis was thromboangiitis obliterans and essential hypertension.

CASE 3.—A woman was admitted to the clinic nine times in all. Previous to the time the cold pressor test was devised, her relevant history was as follows: On her first admission, in 1921, she was twenty-nine years old and her blood pressures in millimeters of mercury were 124 systolic and 76 diastolic. On her second admission, in 1927, she had acute catarrhal cholangitis. Her blood pressures were 120 systolic and 72 diastolic. She was admitted again in 1928, 1929, and 1930. Her blood pressures during these visits ranged from 126 to 135 systolic and from 70 to 85 diastolic. On her sixth visit, in January, 1932, the blood pressure was 124 systolic and 74 diastolic. The cold pressor test revealed an increase in the blood pressure from a basal level of 110 systolic and 80 diastolic to a maximum of 150 systolic and 110 diastolic. Aside from this, examination did not reveal any abnormality. The diagnosis was a prehypertensive state. On her seventh visit, in July, 1932, seven daily readings disclosed a variation in systolic blood pressure of from 114 to 146 and a variation in the diastolic pressure of from 72 to 86. The basal metabolic rate was -12 per cent. On her eighth visit to the clinic, in July, 1933, the blood pressures were 135 systolic and 88 diastolic. On her ninth visit, in July, 1934, six daily readings disclosed a variation in the systolic blood pressure of from 140 to 175 and a variation in the diastolic pressure from 91 to 105. With the cold pressor test the blood pressure increased from a basal level of 128 systolic and 75 diastolic to a maximum of 180 systolic and 110 diastolic. Examination of the ocular fundi revealed narrowing of the retinal arteries, grade 2. The basal metabolic rate was -6 per cent.

A subsequent report will be made of the later developments in this group of normal hyperreactors. At present, we hold to the belief that these subjects have a constitutional abnormality and that essential hypertension eventually will develop in many cases.

Group 3, Essential Hypertension.—In this group were 193 subjects with essential hypertension. The ages varied from twenty-four to sixty-four years. This group was further divided into two groups, the organic type and preorganic type of hypertension. This division was based on

the evidence of the presence or absence of changes in retinal arterioles. The value for the mean rise in the blood pressure in the organic group was 47.2 mm. of mercury for the systolic and 34.3 mm. for the diastolic. In the preorganic group, the mean rise was 34.4 mm. of mercury for the systolic pressure and 25.4 mm. for the diastolic pressure. The low and high values in the entire group were from 22 to 120 mm. of mercury for the systolic pressure and from 20 to 70 mm. for the diastolic pressure. There was some delay in the return of the blood pressure to the previous basal level in both groups. Ninety-seven per cent of the subjects in the organic group and all of the subjects in the preorganic group had abnormal reactions in range. All of the subjects in the organic and preorganic groups had abnormal ceiling values.

COMPARISON OF THE "RANGE" VALUE WITH THE "CEILING" VALUE

An analysis of the ceiling value shows that 98.4 per cent of the normal subjects, with normal range, had a ceiling of less than 145 mm. of mercury in the systolic pressure and that 99 per cent had a ceiling of less than 95 mm. of mercury in the diastolic pressure. Seventy-two per cent of the normal hyperreactors had a ceiling of more than 145 mm. of mercury in the systolic pressure and more than 95 mm. of mercury in the diastolic pressure. There is a definite correlation between the range of the reaction and the maximal rise or ceiling. If, however, the ceiling alone is taken as a criterion, a small group of subjects who have very low basal levels and a high range will be overlooked. If the range alone is taken as a criterion, a small group of subjects for whom, for some reason, proper basal levels cannot be obtained, may be overlooked. Any standard point of differentiation between a normal and abnormal response or level of blood pressure must be arbitrary. From the data at hand, we can conclude that of the group of 388 subjects with normal levels of blood pressure, the ninety subjects with a definitely abnormal range presented presumptive evidence of a hyperreactive vasomotor tonus, as measured by the reaction of the blood pressure. The group of sixty-five subjects with abnormal ranges and with maximal reaction in systolic pressure to 145 mm. of mercury, or more, and in the diastolic blood pressure to 95 mm. of mercury, or more, gave definite evidence of an abnormal vasomotor tonus.

COMMENT

Several points seem to have been brought out definitely by this study. First, the response in blood pressure to a standard stimulation (cold) is fairly constant for the normal individual. Significant changes have not been demonstrated within a year or less. Second, a few "normal hyperreactors" have been observed sufficiently long for essential hypertension to have developed. Third, persistent abnormal pressor responses have not been demonstrated in disease states other than essential hypertension.

We submit the conception that essential hypertension affects only subjects who are hyperreactors. The corollary may not be necessarily true, that essential hypertension affects all hyperreactors. A group of healthy subjects in the later decades of life have been found who have hyperreactions and changes in the retinal arterioles which are indicative of essential hypertension, but who have normal or subnormal levels of blood pressure. A separate report will be made of this important group. A further question arises whether old age per se affects these responses. Our data indicate that normal reactions obtain in aged arteriosclerotic persons whose retinal arterioles do not show changes of hypertension. Subjects with hypertension and arteriosclerosis reveal hyperreactions. This information, while as yet not conclusive, seems to rule out a secondary form of hypertension as a result of the arteriosclerotic process, the so-called senile hypertension.

A demonstrable relationship is established between the ceiling and the response in blood pressure. If a subject has a maximal or ceiling level which exceeds 145 mm. of mercury for the systolic pressure and 95 mm. of mercury for the diastolic pressure, a hyperreactive response to the cold pressor test will be found in 97 per cent of the cases. A ceiling value of 100 mm. of mercury or more for the diastolic pressure shows a hyperreactive response in 100 per cent of cases.

The pressor responses in vasospastic disorders, Raynaud's disease, and neurocirculatory asthenia are inclined to fall in the upper range for normal subjects. In hyperthyroidism and neurocirculatory asthenia, there is an abnormal response in the systolic pressure only. This would lead one to surmise that acquired hyperreactions of nonhypertensive subjects do not attain values reached by the hypertensive subject and that this form of the hyperreactive state may vary with the course of the primary disease.

There seems to be a definite diagnostic value in the pressor reactions in separating the primary and the secondary forms of hypertension. The systolic forms of hypertension seen in neurocirculatory asthenia with tachycardia, in glomerular nephritis, and in hyperthyroidism give responses definitely less than do the preexistent and existent stages of essential hypertension, unless both conditions coexist. The question rises as to whether or not the excessive pressor reaction may be acquired. We have observed one case in which an acute hypertension developed in the course of encephalitis. As far as could be determined, there was no history of hypertension in the ancestry of the patient, but this information was not conclusive. Abnormal reactions have developed in the course of pregnancy, with a subsequent development of toxemia and a return to a normal response following delivery.⁷ Further investigation is needed on this important point.

A conception is here presented that the abnormality of essential hypertension is an excessive response in the blood pressure to intrinsic and

extrinsic stimulation. This abnormality is an hereditary one, which appears early in life and remains during life. When the level of the blood pressure is elevated and clinical degrees of hypertension exist, the reactions then increase with increasing severity of the hypertension. This hyperreactive vasomotor mechanism may be an important factor in the production of arteriolar hypertrophy and in the subsequent development of the organic stages of the disease.

SUMMARY AND CONCLUSIONS

1. A simple, standard test to measure generalized vasomotor tonus has been devised in which ice water is used as a stimulus.
2. This test divides all subjects with *normal* blood pressure levels into two groups: those with "normal" or minimal reactions of blood pressure to the test, and those with "abnormal" or excessive reactions.
3. Ninety-eight per cent of all subjects with essential hypertension have abnormal ranges and abnormal maximal responses to the test.
4. Repetition of the test at intervals indicates that the reaction is a constant one.
5. There is a correlation between the range of the response and the maximal rise of the blood pressure.
6. The reaction probably is based on a generalized vascular constriction initiated through a neurogenic reflex arc.
7. A transition from the prehypertensive state to essential hypertension has been observed in three cases.

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PSYCHOANALYTIC OBSERVATIONS IN CARDIAC DISORDERS*†

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HARVEY'S discovery of the circulation of the blood and of the function of the heart as a pump was so revolutionary, so astounding, and so significant for the materialistic conception of human life that in many ways it may be said to have been the turning point in the career of modern medicine. Many pages have been written in extolling and elaborating its importance, an importance which perhaps cannot be overstated and for which all of us are glad to pay tribute to its modest author.

But in the enthusiasm over the great developments which followed this discovery, medicine lost sight of a nucleus of truth in the pre-Harvian conceptions, which died with his discovery. Because we learned that the heart was a pump we discarded the age-old notion that the heart was the seat of the emotions, and whereas the anatomical and physiological studies initiated by Harvey's discovery have made tremendous advances since his day, the intuitive linking of the heart with the emotional processes was allowed to wither under scientific neglect for over a century until revived by the experimental work of W. B. Cannon.

Such expressions as "heartsick," "hardhearted," "brokenhearted," "chickenhearted," etc., are remnants of the intuitive era of anatomical confusion. But their tribute to the popular overestimate of the heart as an organ expressing emotion is almost entirely ignored by medical science.

If we go back to Avicenna,⁷ for example, we read such intuitive observations as the following: The author is describing the symptoms of love, a condition which he classified among mental diseases.

"In this way," he said, "it is possible, even though the patient may deny his feelings, to identify the person loved, and to base on this knowledge a mode of treatment. The method consists in repeating certain names while the patient's pulse is being read. As soon as the pulse shows any irregularity, the trial is stopped and one begins again. I have tried this method more than once, and discovered through its use the name of the person loved by the patient."

In recent times a few studies of the psychological factors in heart disorders have been written by cardiologists, almost none by psychiatrists. These usually refer with evasive generalities to the "impor-

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†Read at the Chicago Institute for Psychoanalysis, April, 1935.

tance" of psychological factors therein, but unless observed in an individual who shows other and unmistakable neurotic stigmas, the details of the emotional disturbances are rarely linked definitely with the cardiac manifestations.

Numerous forward-looking internists have attempted to understand their patients with cardiovascular disease from the standpoint of psychopathology, but from the point of view of the psychoanalyst, they are limited in their approach by reason of the fact that only the conscious emotional factors are accessible to investigation by the technic ordinarily used. A few cardiologists^{20, 14, 11, 19} point out that the treatment of certain cases of cardiac neurosis require technical psychotherapeutic methods in the hands of an expert; some of them suggest naïvely the occasional desirability of resorting to the aid of a "neurologist."^{18, 2}

Extrasystole has been recognized as being produced by psychic stimuli (Kabakov,¹² Willius²⁷), as is also the syndrome of paroxysmal tachycardia (Kure,¹⁵ Willius²⁷) and that of precordial pain.^{16, 21, 1, 5} Although less frequently clearly psychological, auricular fibrillation and flutter have been regarded as "functional arrhythmias in some cases" (Friedlander and Levine⁹). Even acute dilatation of the heart has been reported¹⁸ as "caused by nothing else but dissociated fear in a patient with cardiac neurosis." The syndrome known as neuro-circulatory asthenia ("soldier's heart") is regarded by many cardiologists as neurosis (Kilgore,¹⁴ Conner,⁵ Willins,²⁷ White,^{6, 8, 25, 26} Boas³).

From the point of view of the psychiatrist, the most gratifying study of the so-called "cardiac neuroses" by a cardiologist is that of Conner.⁵ He distinguished between the psychoneurotic group in which there is fear but no heart symptoms and the neurotic group in which there are heart symptoms without conspicuous fear. He pointed out that in all these cases the psychogenic stimulus is more likely the chief etiological factor rather than an abnormally sensitive autonomic nervous system and that in these cases the stimulus is usually forgotten (in psychoanalytic parlance, repressed). He listed the common (superficial) psychogenic precipitating traumas as: (1) the thoughtless statement of some physician; (2) the knowledge of heart disease and/or sudden death in the family or friends; (3) the occurrence of some sudden symptom such as pain, which focuses attention on the heart; and (4) a profound emotional disturbance as in "shell shock." He stated very definitely that treatment belongs essentially to the realm of psychotherapy.

The close interrelationship between organic heart disease and psychic stimuli are well recognized in angina pectoris, and well summarized in a recent paper by Katzenelbogen¹³: "Clinical and anatomopathological observations brought to light the concept that the morbid manifestations of such organic disease *par excellence* as angina pectoris appear to be controlled by a functional factor. Such a belief

has its basis in the fact that one finds at post-mortem examination sclerosis of the coronary artery in persons who never had anginal attacks. Moreover, in certain patients who did suffer from typical attacks of angina pectoris and displayed evidence of marked excitability of the vegetative system, the anatomical examination did not reveal lesions in the myocardial vessels; nor could any lesion of the vegetative system be discovered."

PSYCHIATRIC STUDIES

Recently there have been a few reported studies of cardiovascular disorders from the psychiatric point of view. Wolfe²⁶ reported three cases of functional cardiovascular disease and reviewed briefly some previous psychiatric observations of these conditions. He noted the very frequent occurrence of intense repressed hatred, resentment, and strong guilt feelings in patients with increased tension and angina pectoris.

Braun⁴ developed the thesis that the heart was the specific organ of anxiety, apparently failing to recognize the complex psychological features associated with anxiety. He devoted an entire chapter of his book to the diagnostic significance of the anxiety dream. MacWilliam²⁷ reported some physiological observations of the increase in blood pressure and heart action during sleep and in dreams. In Wolfe's study of the dreams in 100 cardiac patients he found the majority related to falling, to jumping, or to some life-threatening situation and that these occurred, in most cases, only at the time of an exacerbation of the cardiac illness.

Galli¹⁰ has reported a series of psychiatric investigations of the "cardioneuroses" and "circulatory neuroses."

PSYCHOANALYTIC OBSERVATIONS

It is greatly to be regretted that some of the rich clinical material so elaborately studied from the physical and descriptive sides by the cardiologists could not similarly be subjected to penetrative psychiatric study. This lack of cooperation between cardiologists and psychiatrists is truly deplorable because it hinders both of them and retards scientific knowledge. The cardiologists acknowledge that they need psychiatric help in the understanding of their cases, and the psychiatrists would profit greatly to learn more of the ways in which thwarted instinctual demands are organically rather than behavioristically expressed.

Perhaps it is partly due to the fact that the psychiatrists have immolated themselves too much. They have talked about "schizophrenia" and "negativism" and "delusions" until the internists perhaps conclude that psychiatry has not advanced beyond the early days of preoccupation with the "insane" and is using an appropriate

vocabulary. The result is that many internists have rather scant conception of the advance which has been made in our ability to determine the precise quality if not quantity of repressed emotion. Significant and valuable as are our advances in the knowledge of the heart as the result of the electrocardiograph, progress in psychological investigation has been even more advanced and revolutionary. Cardiologists who would deplore or be amused by the use of such vague terms as "heart trouble" or "heart stoppage" on the part of psychiatrists use equally naïve, vague, and unscientific designations for emotional states, and do so with complete obliviousness of how empty and unprecise they sound to one familiar with methods of careful emotional evaluation. To be sure, many psychiatrists are also guilty of using such vague and meaningless terms but this does not invalidate our thesis any more than does the fact that some cardiologists scoff at the electrocardiograph discredit its great value.

Of course the greatest single step in the more definitive recognition of specific emotional factors and vectors is the appreciation of Freud's concept of the unconscious. Intuitively every thoughtful person is aware of the existence of unconscious emotional forces in his thinking, acting and feeling, but there are strong repressive forces striving to deny it the consideration it deserves. Moreover, doctors in particular have been traditionally educated, unfortunately, to distrust their intuition.

The painstakingly extended field of psychoanalysis, however, has uncovered a mass of material which has given us a new orientation in the understanding of the emotions (just as Cannon's researches have enlightened us relative to the physiological machinery used in expressing these emotions). Freud discovered and taught us a technique for investigating the unconscious roots of conscious emotional and behavioristic expressions so that now in any particular case it is theoretically possible to be precise and explicit as to the deep psychological trends present, let us say, in a case of chronic endocarditis.

The practical difficulties in carrying through such an investigation are, unfortunately, very great. Clinical cooperation is rare, research funds are few, the expense in time and money is large. Hence it is only an exceptional case in which we have the opportunity to study the emotional life of the cardiac invalid beyond the superficial descriptive phase. Occasionally a cardiac patient comes under the scrutiny of psychoanalysis—perhaps for quite other than the cardiac symptoms. Under such circumstances a great deal is learned about the patient's emotional life, conscious and unconscious, and some of this naturally relates to the illness. In some instances it appears to relate so specifically to the illness that we may fairly say that the emotional factors perhaps enter into the etiology of the illness. This is not a

fact yet—it is not even a hypothesis. It is only a suggestion of a possibility which the clinical reports of observant cardiologists have already intimated as indicated above.

As yet, however, the material is much too limited for us to draw any conclusions. Very few psychoanalysts have reported the cases they have seen. This is partly due to the fact that they are so few in number and partly, upon the other hand, to the inconclusive nature of the findings. Psychoanalysts can study only a relatively small number of patients because each case requires such an enormous amount of time, and psychoanalysts who have spoken to the present writers about such cases usually add that it seems inconclusive and not particularly valuable to relate the details of one or two cases which they have studied in the light of the hundreds of thousands of cardiac cases which are being studied clinically.

The authors of this paper feel that we should not be deterred by these considerations from at least making a start in the recording of such observations. If it has no other effect, perhaps it will stimulate the development of some research in a cooperative way between the cardiologists and the psychoanalysts.

One of the cases reported in the psychoanalytic literature²² is the following:

A woman, thirty years of age, had a "heart neurosis" of several years' standing, evidenced by attacks of violent palpitation which lasted for hours and were accompanied by painful anxiety. Occasionally the pulse ceased, and it was necessary to revive her with camphor injections, black coffee and champagne.

Examination showed nothing beyond a slight irregularity and acceleration of the pulse. There was a scarcely perceptible struma parenchymatosa. Stekel suggested psychotherapy, to which she "was all the more ready to agree, having obtained no relief from all her water-cures, strophanthus, digitalis and caffeine."

She began by saying that her early life had been uneventful, that she had married the man she loved when she was twenty-two years old and that he had been a model husband. She was sexually satisfied and was the mother of three children. The nervous condition began about four years after the marriage and was attributed to overwork, responsibility, worry and overexertion about household affairs. In the second interview she described the last and worst attack she had had.

This had occurred on the anniversary of her wedding day. Her husband's sister and her husband, Mr. X., had visited the patient and had quarreled violently, Mr. X. charging his wife with having a love affair with the family physician (the same one with whom the patient had become dissatisfied when she came to see Stekel). It developed that the patient had formerly been interested in this doctor and was terribly excited when it was suggested that this sister-in-law, of whom she had long been jealous, was the real object of the doctor's love. She fell down with a loud cry and was shaken with convulsions.

In later interviews the patient told of three similar attacks, all of which had taken place on her own and on friends' wedding days. She then admitted dissatisfaction with her marriage, saying that her husband was unfaithful, unkind, and

²²It is only fair to say that Stekel, while regarded as intuitive, is not regarded by some as scientific in all of his work and is not a recognized psychoanalyst, i.e., in the sense of being a member of the International Psychoanalytic Association. This does not in our opinion disqualify the present observation.

did not appreciate her and that he suffered from ejaculatio praecox and often left her sexually unsatisfied. Finally she confessed that she had not really married her husband for love, but because she had been jilted by the man she loved and because she was greatly attracted to her future husband's sister, Mrs. X. All in all, her marriage had been a bitter disappointment.

In the further course of the analysis the patient recalled an incident of her childhood when she was six or seven years old. A lodger who lived with her family had showed her his erect penis, and she had been impressed with its immense size which she had exaggerated in her mind in the years that followed until she was greatly disappointed on her wedding night to find her husband's normally developed penis did not approach the gigantic size of the one in her imagination. She had wept for hours with palpitations and feelings of anxiety and had been entirely anaesthetic sexually.

When this childhood recollection came back to her the patient had an attack of palpitation, anxiety, and spasms and could not continue with the interview. The next day, however, she felt completely relieved and continued to improve until the attacks and palpitations entirely ceased. Six years later she was still well and happy, although she had had to face a severe psychic shock in a business bankruptcy. She had gone through two confinements easily and was contented in her marriage.

Stekel also cited the case of a man fifty-one years old.

A man of Herculean proportions who had never known a day's illness until one night he awoke with a feeling of being strangled. He fought for his breath, feeling that he was dying. The attack soon passed off, and he thought it was due to a heavy supper the evening before. A few nights later, however, he had another attack and from then on they occurred frequently in the day as well as at night. He consulted a physician friend who diagnosed his illness as incipient arteriosclerosis and told him that with care he might live two years longer. On the advice of his friend the patient entered a sanitarium. He became more and more dejected and felt that his death was approaching. Eventually he came to Stekel for treatment, in the course of which he discovered that the heart attacks originated in a severe psychic conflict. He had lost the woman he loved, and with whom he had had a liaison for five years, to his best friend. For many weeks prior to the onset of his symptoms he struggled with the thought that he must strangle his friend for this betrayal. The analytic treatment was successful, and the attacks entirely ceased. Ten years later the patient was still "perfectly well, happily married, and at the height of his creative powers."

In our own psychiatric practice we have seen many patients whose chief symptoms seemed to be referable to the heart. The presenting symptoms of precordial pain, dyspnea, palpitation, and tachycardia engage the patient's attention, and he in turn uses them to engage the physician's attention. They are his passport or ticket of admission to the land of illness with all its restrictions and its advantages. Some of the most alarming cases we have seen were in part the result of unfortunate suggestion on the part of well-meaning physicians who, themselves alarmed at some of the patient's symptoms, prophesied a serious outcome or showed so much solicitousness and anxiety over their discovery as to gratify to the fullest extent the patient's hopes and fears. The patient becomes enormously frightened but also very much gratified to find that at last he is able to make somebody come to his aid with a proper degree of concern. Many internists

have called attention to this mistake on the part of the examining physician (Shirley Smith, Conner, Reid, Willius, Kilgore). Occasionally we are able to find some conscious reason for the fear and for the excessive need for the protection afforded by the physician. Occasionally, also, organic factors are actually present and advanced to such a point where even the discovery and correction of the emotional factors is of secondary importance. For example, one patient who was able to escape from the necessities of married life with a husband whom she did not love but could not afford to leave developed a heart affliction (chronic mitral disease) which had apparently grown gradually over many years but which by the time we saw her was actually so far advanced as to be irreversible.

Others of our cases have been more accessible to penetrative psychological study. One, for example, was a man, sixty-one years of age, with a definite organic heart affliction which seemed to us to bear a definite relation to his psychopathology.

CASE REPORTS

CASE 1.—A man, aged sixty-one years, had been subject for more than four years to attacks of severe chest pain which radiated down both arms to his wrists and was accompanied by diaphoresis. He had been to many doctors, all of whom agreed as to the seriousness of his illness and counselled rest. He began to have violent headaches. He was living very quietly; for a year and a half before consulting us he had given up work and followed a careful regime of breakfast in bed, staying in bed until noon, then dressing for lunch, resting several hours after lunch, going for a drive of a few miles in his car driven by a chauffeur, and then returning home to bed once more. In spite of all this he complained of never feeling or sleeping well.

Examination showed he had a generalized arteriosclerosis with symptoms indicating involvement of the cerebral and coronary arteries.

Coincident with or even antedating the onset of this patient's anginal seizures, he had begun to feel vaguely nervous, uneasy in the company of other people and troubled by dreams of the past (especially of old business associates) at night. For many years he had been troubled by severe constipation and a variety of other "colonie" complaints. By the time the patient came to us, his nervous complaints were preponderant and had attained the magnitude of an incipient paranoid psychosis. He confided in the doctor that he had masturbated and believed that all of the townspeople knew of his habit and were talking about him. He was also greatly troubled by erotic dreams in which an actual male bedfellow would usually become the object of his advances while he slept and often reprimand him for the advances.

The patient was a small-town wealthy business man, a bachelor in the present. His entire past history (including a predilection for prostitutes, a love for male company in hotels, and an absence of sustained interest in any woman) pointed to strong unconscious homosexual propensities, against which he had waged a successful struggle until recently. He had latterly shown a tendency to become excessively fond of young male employees in his home and although there had never been any history of overt homosexual practices, the approach of these inclinations to consciousness was undoubtedly responsible for some of the fear represented by the symptoms of the illness.

It is interesting that this individual showed a remarkable improvement in all of his symptoms as soon as he was admitted to the sanitarium (where, of course, he was protected against any such temptations). His paranoid trends resolved entirely. While there was considerable evidence of anatomical coronary artery disease, he exhibited a functional improvement in his cardiac status that was truly surprising. Whenever this patient contemplated returning to his home, his symptoms increased in severity. It was evident that, aside from the routine sanitarium therapy, the patient had derived considerable benefit from separation from the influences which had been stimulating his homosexuality excessively. He was able to make an acceptable transference to a doctor and thus relinquish much of his need for punishment and his paranoid and hypochondriacal defenses against homosexuality.

The fact of the patient's improvement was unquestionable, although it is difficult to assign to the psychological factors in his illness their exact proportions. It is, of course, entirely possible that the somatic and visceral disturbances incident to the presenium served as the initial traumata which broke down a well-sealed psychological system and then assumed definite rôles and were elaborated within that system.

In another case, the psychological investigation was carried much deeper.

CASE 2.—A male, aged forty years, was studied over a period of several years. He had persistent and distressing cardiac symptoms in the discussion of which he spent many hours. He complained of precordial and presternal pain with the radiation of the pains down the left arm to the fourth and fifth fingers. We do not believe he had ever read any textbook descriptions of angina pectoris, but there is considerable probability that he had known one or two men who had suffered from it, and his symptoms were strongly suggestive of it. He professed to be so distressed at being awakened in the night by these pains and the fear of death that he went to fully a dozen physicians over the country, most of whom told him they could not find anything organically wrong with his heart, and a few of them frightened him severely by looking grave, shaking their heads ominously, and telling him he was going to have to be careful. In order to eliminate the possibility of a mistaken diagnosis he was examined by several of our internists. An electrocardiogram and a roentgenogram of the heart were entirely normal. This was not, therefore, a case of organic heart disease, but only one in which the patient thought he had heart disease and professed that he suffered cardiac pain. Very early in the psychoanalytic conferences he commented on the fact that this pain seemed to develop at certain times when he felt guilty about sexual misadventures, and he spoke of the common knowledge that death sometimes follows intercourse. (This, of course, one cannot dispute. The fact is also referred to by many. Weiss²⁴ refers to the observation of anginal attacks "regularly" following coitus.)

The pain, he said, seemed to take the form of the letter *S*, with which his first association was that the name of the girl with whom he had had his guilty affair also began with *S*. This also gave rise to a train of thoughts suggested by the words "sin," "sick," "sorry," "sex," "syphilis," etc. He also noticed that having confessed the details of this episode the heart symptoms disappeared for a time. They came back, of course, and it was many months afterward that the deeper meaning of his heart attacks was discovered. This occurred as follows:

For several weeks he had been very much more able than usual to deliver free associations and less obliged to harangue the analyst as was his wont about his heart,

his selfish wife, the futile and endless psychoanalysis, etc. Then one day he reported the following dream which threw light on his reiterated complaints of pain in the heart, with fear of death, etc.

The dream was short. It was only that "*Sammy*" Insull was there and had died or was about to die on account of heart trouble and the cause of it was an obstruction in his heart which seemed like a blocked valve in a carburetor.

His associations to the parts of the dream were: "Insull is a persecuted man; they have just smoked him out of Greece and brought him back to this country, but it is only because the politicians want to save themselves. They say he is a rascal, but I sympathize with him. Perhaps I identify myself with him because I am hounded. [And because you have heart trouble?] Yes, he is sick, and I am sick. [But what is he charged with?] With taking other people's money. With trying to get everything he could get his hands on, I guess."

It was pointed out to the patient that he minimized the charges against Insull of having misused funds, misrepresented facts, and taken so much from so many people. In this sense the identification was quite clear. The patient felt guilty on account of his own grasping, stealing, sucking propensities, and defended these propensities in Insull with whom he identified himself. In the dream he called Insull "*Sammy*" which bespoke a friendliness and intimacy which he rarely assumed with anyone except himself. The carburetor, as he said, is the intake organ for the automobile and represented his own sucking mouth. Carburetors suck in air and gasoline, and this sucking was blocked, and it was (in the dream) this blocking that was breaking down the heart.

In order to get a complete idea of the case it would be necessary to summarize the whole life history, and, as this would be a practical impossibility, we shall content ourselves by saying that he had been an "oral character" all his life; that is to say, the thwartings of his childhood had been such as to greatly sharpen his appetite for love and this love which he demanded and obtained from many people or at least wanted to do so. It is important in this connection to mention that he was not weaned by his mother until he was almost three years old, and as he said himself, "I can see that emotionally I was never weaned." He betrayed this peculiarity in many ways as well: sucking and puckering up his lips, smoking and chewing excessively and talking and arguing a great deal. Whenever he would approach a realization of certain more socially reprehensible activities such as fellatio, he would go into great panic, deny them absolutely (before he had even been accused), sulk, and denounce psychoanalysis; but, on the other hand, at such times the heart symptoms would be gone.

The implication of the above dream is, with this background, quite intelligible, even to one whose experience with dreams is relatively limited. His unconscious is trying to say in picture language something like this: "Sam Insull is like me. He is a great man, but he is persecuted. Like me he is utterly disappointed. He tried to get everything, and lost. I, too, feel disappointed and guilty. The pain in my heart represents a punishment for this guilt and also represents my disappointment in the blocking of my intaking capacity (carburetor)."

CASE 3.—A third case, which we present through the courtesy of Dr. Edwin Eisler, of Chicago, was that of a man, forty-one years of age, who was engaged in an active law practice. His chief complaint was periodic precordial heart pain, with radiating pain down the left arm. These attacks at first seemed to be related to slight effort but were later noted to be unassociated with any specific activity. The

*Dr. Leon Saul, of Chicago, informed us upon reading this case that he had had one so nearly identical in many respects that the case history would sound almost like copy. This even went so far as to include the identification with Insull, dreams about him, defense of him, etc. In Dr. Saul's case the mechanisms seemed to be quite similar to those reported here, and for this reason, as well as some reasons of professional discretion, it seemed undesirable to give further details of Dr. Saul's case.

Franz Alexander also cited some cases psychoanalytically studied, one of which was of particular interest because of the paradoxical outcome.*

Summary of Psychoanalytic Observations.—The psychoanalytic studies of cardiac cases are too few for us to come to any definite conclusions, but some suggestions from the cases reported above might be crystallized around the following outlines.

It would appear that heart disease and heart symptoms are (sometimes) a reflection of strongly aggressive tendencies which have been *totally* repressed. Characteristically they appear in a man who was strongly attached emotionally to his father and often more or less definitely hostile to his mother. The conscious affection for the father completely obliterated the deeply buried hostilities for him. If, then, the father has heart disease or symptoms of heart disease, it is very typical for the patient to include these symptoms in his identification with the father but to carry out the inexpressible patricidal impulses reflexively by unconscious focal suicide. It has been suggested by some of the analysts who have studied these cases that this identification is not with the father so much as with the father's preferred love object, i.e., his wife, the patient's mother, and that in this sense the heart disease is at the same time symbolic of the "broken-heartedness" of disappointment and of the womb, i.e., the internal sex organ of the woman. At any rate, that the aggressive tendencies seem to be important in the development of heart affections is supported by the fact that coronary sclerosis is so enormously more prevalent among men than among women.

These speculations must not be construed to be other than a most tentative hypothesis with which to compare further observations and upon which to base only some projects for specific research investigations.

SUMMARY

We have attempted to show that the emotional factors which tradition and clinical experience alike ascribe to the heart and particularly to disorders of the heart are capable of more explicit designation. Opportunity for cooperative research between cardiologists and psychoanalysts is lacking and is sorely needed. We have presented here some opinions, some intuitions and some case observations. We have

*This patient was a forty-year-old physician, himself a heart specialist! He suffered from a phobia with the definite content of fainting or dropping dead if he were alone—especially on the street or when he left home to visit his patients. In such situations he had attacks of fear connected with palpitation and precordial anxiety. His phobia interfered with his practice to an increasing degree so that his wife had to accompany him on his visits to patients.

Psychoanalysis revealed an extreme longing for and regression to the infantile period in which he could not yet walk and had to be led by his hand. The analysis of one and one-half years succeeded in overcoming his fear to a great extent. He was able to resume his practice and was successful in it again for a period of two or three years after the end of the analysis. Then one day while walking on the street he dropped dead, and the post-mortem examination showed the presence of organic heart trouble!

even hazarded a very tentative hypothesis relating to the deeper psychology in some forms of heart disease. Our data are entirely insufficient to prove anything; they only suggest that these psychological factors are sometimes of importance in the development of cardiac pathology. Whether they act by way of bringing about a disordered function which in turn becomes established as organic pathology or in some more direct way, we have no evidence or opinion. The therapeutic effect on the patient of the psychological investigation is also to be regarded thus far as a secondary, though fortunate, corollary of the investigational process.

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THE INCIDENCE OF BLOOD VESSELS IN HUMAN HEART VALVES*

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THE experiments described in this paper were planned for the purpose of determining the incidence of blood vessels in the valves of human hearts which, so far as could be learned from clinical histories and clinical evidence, were free from endocardial disease and its common precursor, rheumatic fever. We assumed that the valves in such hearts would be within normal limits. The work had scarcely got under way, however, before it was observed that some of the valves bore scars of various kinds and, in a few, unmistakable evidence of active or healed valvulitis was present. This report deals with the frequency of occurrence of blood vessels in human heart valves and with the relationship of those vessels to various scars and lesions which were encountered.

Since the middle of the last century when Luschka¹ first described blood vessels in human heart valves, there has been controversy concerning their existence and their significance when present. Luschka believed that all atrioventricular and semilunar valves were vascularized normally. Several years later Rosenstein² confirmed Luschka's work while Joseph³ and Cadiat⁴ denied it. Another group of workers, Kölliker,⁵ Heule,⁶ Frey,⁷ Sappey,⁸ Cruveilhier,⁹ and Coen¹⁰ admitted the presence of blood vessels in the atrioventricular valves, but denied Luschka's claim of their existence in normal semilunar valves. Langer,¹¹ on the other hand, observed vessels in diseased valves only and not once in a normal valve. He was the first to point out that, in the atrioventricular valves of adults, blood vessels extended only so far as there was muscle, but that in fetal hearts and those of newborn children the muscle fibers and vessels passed to the free edge of the valve and regressed with age. Later, Davier,¹² Königer,¹³ Odinzow,¹⁴ Nussbaum,¹⁵ and Tandler¹⁶ supported the main conclusions of Langer.

Rappe¹⁷ described the architecture of vessels in the mitral valve particularly and because of some constancy in structure he suggested the possibility of some vessels being of noninflammatory origin. He also recognized the frequent coexistence of valvulitis.

Köster¹⁸ was the first to suggest the embolic origin of valvular endocarditis and his theory was later supported by Rosenow.¹⁹

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In more recent years MacCallum²⁰ demonstrated vessels in the basal third of the atrioventricular valves in dogs. In human hearts Bayne-Jones²¹ found vessels in the valves of three of a series of fourteen grossly normal hearts. He also found a richer vascularization of the valves of pigs' hearts. Gross and his coworkers,^{22, 23, 24, 25, 26} (1921-1928), using barium sulphate gelatin as an injection mass, succeeded in injecting blood vessels in at least one of the valve leaflets in 18 per cent of a series of 700 human hearts. After a careful clinical and pathological study, however, they considered only 2 per cent—fourteen hearts—of the injected specimens normal. More recently²⁷ these workers have stated that, if blood vessels do occur at all in human heart valves, they are most infrequent.

Kerr and Mettier²⁸ and Kerr, Mettier, and McCalla²⁹ have obtained the highest percentage of injection of heart valve vessels reported to date. These workers used India ink and demonstrated the presence of capillaries in one or more valves of 36 per cent of twenty-eight normal human hearts. Moreover, they found vessels in every instance in 242 pig hearts and five beef hearts. They feel that their results are in harmony with the embolic origin of valvular endocarditis. Wearn³⁰ in 1928 demonstrated a rich capillary supply in the atrioventricular and semilunar valves. A preliminary report^{*} of the present study was made in 1930.

It is obvious, therefore, that no agreement exists in the literature at the present time as to the frequency of occurrence of blood vessels in the heart valves or whether they ever occur in normal valves. Some of the lack of agreement in the results reported may be accounted for by the difference in the type of hearts selected for study, but a more probable explanation may be found in the wholly different methods employed by the various workers in injecting the vessels in the valves.

In this study one hundred human hearts were used, which were obtained from consecutive necropsies after the elimination of all cases with any history or clinical evidence of endocarditis either in the past or during the final hospital stay. Neither was there any history or evidence of rheumatic fever or allied conditions. Arteriosclerosis appeared in the diagnosis in twenty cases. Of these, fourteen were recorded as having "chronic myocarditis," supposedly due to sclerosis of the coronary arteries, and five died of heart failure. With but two exceptions all those patients with "chronic myocarditis" were over sixty years of age. The most common primary causes of death were respiratory diseases including pulmonary tuberculosis, malignant growths, cerebral hemorrhage, sequelae to surgical operations, and accidents.

METHOD

The method of injection used in our work was as follows: Immediately after each heart was received, it was washed and massaged gently in order to remove as much blood as possible from the coronary vessels. It was then kept moist in the

^{*}Bromer, A. W., Zschiesche, L. J., and Wearn, J. T.: *J. Clin. Investigation* 7: 487, 1929. *Tr. Am. Clin. & Clin. Assoc.* 47: 1, 1931.

ice box for twenty-four to forty-eight hours to allow the rigor mortis to pass off. In a few instances the hearts were three or four days post mortem when injected. Immediately before injection the heart was placed in water at about 38° C. and gently massaged until completely free from rigor. Cannulas were tied into the coronary arteries and connected by a Keyes stopcock with a suction apparatus on one side, and on the other with a bottle containing the injection mass (Fig. 1). Suction was applied to the arteries in order to remove as much air as possible and then by a turn of the stopcock, India ink was injected at a pressure of 220 mm. of Hg when the hearts were from adults, and 120 to 150 mm. of Hg in children's hearts. Freshly opened Weber's India ink diluted with an equal part of distilled water proved to be a satisfactory injection mass and easily penetrated the capillaries. During the injection, the heart was massaged while immersed in a tank of 0.85 per cent saline solution at a temperature of 38° C. As far as possible, all leakage from the extracardiac branches of the coronary arteries²¹ in the cut edges of the pericardium and around the great vessels was controlled with hemostats.

After injection was completed, the hearts were carefully examined grossly for endocardial, myocardial, and pericardial changes. They were placed in 10 per cent aqueous formalin for fixation. The valves with their rings were removed by dissection and cleared by the Spalteholz method.²² After clearing, the valves were studied

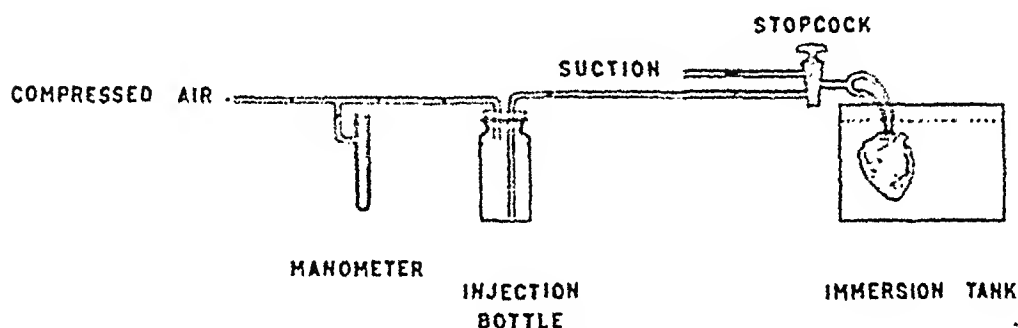


Fig. 1.—Diagram of injection apparatus.

grossly and then submitted to examination with a binocular binobjective microscope in a careful search for blood vessels. This procedure revealed vessels in many instances which had not been visible previous to the clearing. Sections were later taken from various places in many of the valves and from the myocardium of each heart. Those valves which appeared wholly normal on careful gross inspection, showing no scars or thickening, were not sectioned in every instance. Hemotoxylin and eosin, Mallory's connective tissue, and van Gieson's stains were used in staining sections for study.

BLOOD VESSELS IN HEART DISEASE

In this work a valve was considered as having blood vessels in it only when the vessels extended clearly beyond the valve ring into the free portion of the leaflet or cusp. This free portion of the valve is, strictly speaking, the true valve, inasmuch as it is the part that prevents the backflow of blood. In some instances, muscle fibers extended into the free valve, but when they extended well into the free portion they were considered as part of the valve. In no instance did any of our sections include the valve ring as outlined in the text figures by Gross and Kugel.²⁷ Indeed, we considered the ring as ending at a line drawn

transversely or perpendicularly across the main axis of the valve at the most distal point of its basal attachment. Using this standard, we found blood vessels in one or more valves in eighty-six of the one hundred hearts studied. After completing the microscopic studies, however, twelve hearts showed evidence of valvulitis, either active or healed. In the remaining eighty-eight hearts, gross and microscopic search failed to reveal any evidence of healed or active inflammation. It is possible that in the past there may have been valvulitis that healed without scar formation, or with eventual disappearance of the scar. The absence of inflammatory changes at the time of death, therefore, is not conclusive evidence that a valve has been free from disease. In the twelve hearts with evidence of active or healed valvulitis, the mitral valve was the seat of the lesion in nine instances, and the aortic valve in the other three. Only six of the mitral valves were vascularized, and no blood vessels were found in the aortic valves. Thus, six of the twelve diseased valves were avascular.

Blood vessels were found in the leaflets of one or more valves in seventy-four of the remaining eighty-eight hearts. The number of valves in each heart showing injected vessels varied as follows: In seven hearts, all four valves were injected; in sixteen hearts, vessels were demonstrated in three valves; twenty-six hearts had injected vessels in two valves, while in the remaining twenty-five hearts a single valve showed injected vessels. In twelve valves, uninjected vessels were found by microscopic examination.

The frequency of occurrence of blood vessels in each of the valves is shown in Table I.

TABLE I
EIGHTY-EIGHT HEARTS WITHOUT VALVULITIS

VALVE	VASCULARIZED VALVES	
	NUMBER	PER CENT
Mitral	68	65.9
Tricuspid	65	63.6
Pulmonary	25	28.4
Aortic	14	15.9

The distribution of the vessels varied greatly in the different valves, and there was no uniform arrangement in the individual leaflets. For this reason, the findings in each valve will be presented separately.

MITRAL VALVE

The vessels in the mitral valve were located just beneath the endocardium on the superior surface of the leaflets. Small arteries, arterioles, capillaries, and veins were found in this region. Infrequently one found vessels running up the papillary muscles and through the chordae tendineae to pierce the valve leaflets and anastomose with those on the superior surface. Such vessels almost always occurred in the shorter

papillary muscles and chordae tendineae which were attached to the inferior surface of the valve near its base. Veins extending several millimeters below the basal margin of the aortic leaflet were found in several specimens which were injected under low pressure through the coronary sinus.

The various types of distribution of the vessels encountered in the leaflets are shown in Figs. 2, 3, and 4, which are photographs of mitral valves. The most common arrangement is that shown in Fig. 3 where the vessels extended from 3 to 7 mm. beyond the edge of the ring into the



Fig. 2.—H-4-B. Normal mitral valve from subject aged fifty-three years. Magnification $\times 2$.

free leaflet in a rich network of fine caliber as shown in this figure. Many of these small vessels ended blindly, showing that their complete course had not been outlined by the injection mass. This type of distribution was found in less than half of the valves. The other extreme with a rich vascular supply from several arterioles is shown in Fig. 2 on the aortic leaflet. All stages between these two extremes were found.

Less commonly, two small arteries descended from the base of the aortic leaflet along or near the lateral margins to meet near the line of closure. They gave off branches en route, some of which formed delicate anastomoses with other vessels and at times reached the free margin of



Fig. 3.—H-47-B. Normal mitral valve from subject aged fifty-eight years. Magnification $\times 3$ (approximate).

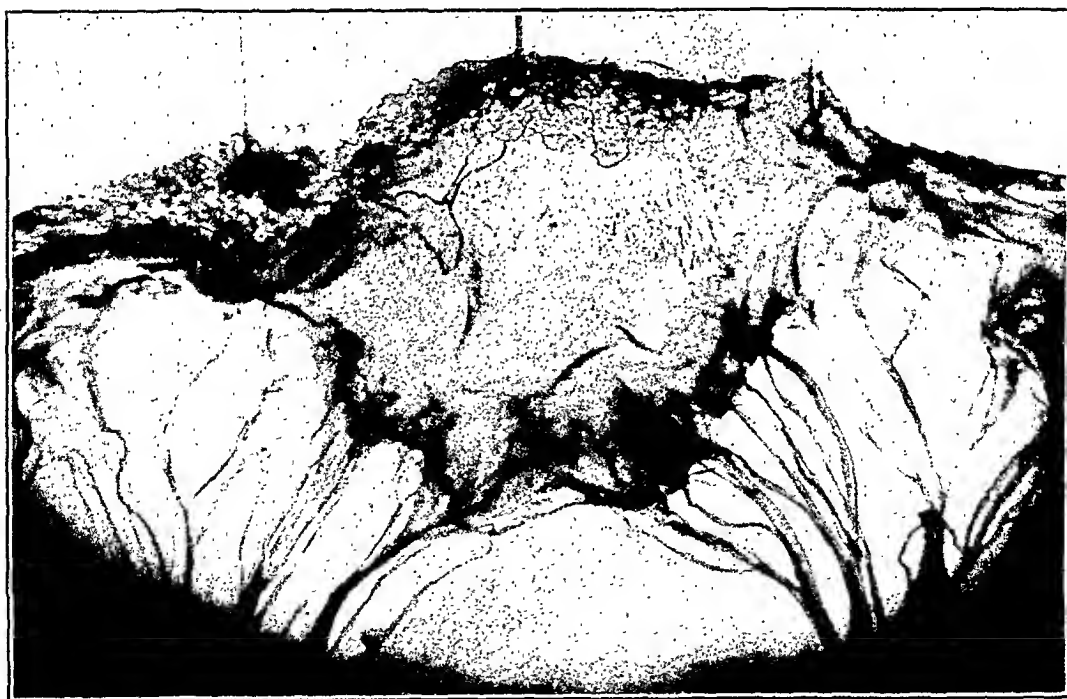


Fig. 4.—H-105-B. Normal mitral valve from subject aged fifty-five years. Magnification $\times 3$.

the valve. There was no constant distribution of the vessels on either leaflet and the relative frequency of occurrence of vessels was approximately the same in the two leaflets.

TRICUSPID VALVE

The vessels of the tricuspid valve were, as a general rule, of finer caliber than those in the mitral. Many of them were not found until the valve had been cleared. In about 40 per cent of the vascularized tricuspid valves, the vessels extended from the base to about one-half the distance to the free margin, while in the remaining ones the vessels were a few millimeters in length. The distribution of the vessels was even less constant than in the mitral valve (Fig. 5).



Fig. 5.—H-71-B. Normal tricuspid valve from subject aged fifty-six years. Magnification $\times 2$.

PULMONARY VALVE

In the pulmonary valve, the arteries were of extremely fine caliber. They emerged from the line of attachment of the valve at numerous points, sometimes from the commissures between the cusps and at other times from the base (Fig. 6). The arteries immediately branched into a meshwork of capillaries, the distribution of which was limited for the most part to the lower two-thirds of the cusps. In no instance did they extend to the corpus arantii. Muscle fibers were found rarely in this valve. Vessels were found in one cusp only in seventeen valves, in two cusps in seven instances, and in a single heart all three cusps contained blood vessels.

AORTIC VALVE

In the aortic valve the vessels were, in many instances, of larger caliber than those in the pulmonary valve. They arose as branches of the arteries in the richly vascularized commissures and entered the cusps



Fig. 6.—H-78-B. Normal pulmonary valve from subject aged eighty-four years. Magnification $\times 4.5$.

to extend horizontally across them, at times along the line of closure and, in some instances, reaching the corpus arantii (Fig. 7). No muscle fibers were found in any of the sections examined microscopically. In twelve specimens, the vessels were limited to one cusp, in one specimen to two cusps, and in one heart all three cusps showed injected vessels.

RELATION TO AGE

It is interesting to note the relative incidence of vascularized valves in the various decades of life. This is shown in Table II.

It should be pointed out that the technic for injection of infant hearts is less satisfactory than that for adults in that the coronary arteries are so small that cannulation of them is not practical and the injection must be made through a cannula in the aorta. This fact may account for the lower percentage of injected vessels in the first decade. Otherwise, the incidence of vascularized valves in hearts is essentially the same in all decades. In the first decade, the ages of the individuals whose heart valves contained blood vessels were two days, seven days, nineteen months, three years, four years, and five years.

In view of the former contention of Gross and Kugel and others that the presence of blood vessels in a heart valve predisposes to valvulitis,

TABLE II
INCIDENCE OF BLOOD VESSELS IN NORMAL VALVES IN DECADES

AGE PERIOD	NUMBER OF HEARTS INJECTED	NUMBER HEARTS WITH VASCULARIZED VALVES	PER CENT
First decade	11	6	55
Second decade	2	2	100
Third decade	10	7	70
Fourth decade	9	7	78
Fifth decade	12	12	100
Sixth decade	24	20	83
Seventh decade	10	10	100
Eighth decade	5	5	100
Ninth decade	5	5	100

it is interesting to compare the frequency of occurrence of blood vessels in a valve to the incidence of endocarditis in that valve. It is generally accepted that the mitral valve is the most common seat of endocarditis and that the aortic, tricuspid, and pulmonary valves follow in the order named. Endocarditis in the pulmonary valve is a relative rarity although, as shown by Holsti³³ and Swift,³⁴ careful microscopic study may reveal the presence of inflammation when gross evidence of such is lacking.

The mitral valve, the most frequent site of valvular endocarditis, shows practically the same incidence of vascularization as the tricuspid valve. Aside from the mitral valve, there is no further agreement between the frequency of occurrence of blood vessels and the incidence of valvulitis in a given valve. In the aortic valve, for instance, which stands next in frequency to the mitral as a site of valvulitis, blood vessels were encountered less frequently than in any other valve. The surprisingly high incidence of blood vessels in the tricuspid valve, which, indeed, is practically as high as that in the mitral, is of great interest, for the incidence of endocarditis in this valve is considerably less than in the

mitral. Finally, the presence of vessels in twenty-five out of eighty-eight pulmonary valves is out of all proportion to the incidence of endocarditis in this valve. The clinical occurrence of pulmonary valvulitis is rare, and acceptable microscopic evidence of its presence is uncommon.

Such gross lack of agreement in the incidence of blood vessels and valvulitis in a given valve is suggestive evidence that the mere presence of blood vessels does not predispose to valvulitis. This evidence is of greater import if the vessels occur normally in the valves, for in that event endocarditis, if embolic in origin, should occur with the same frequency approximately as do the vessels in the valve. But evidence of this sort is not conclusive, even though strongly suggestive.

A great many scars of a noninflammatory nature were found in the routine examination of the valves. Grossly, they appeared as a simple



Fig. 7.—H-4-B. Normal aortic valve from subject aged fifty-three years. Magnification $\times 2$.

thickening in the valve or as sclerotic plaques. These scars were both proliferative and degenerative, but in neither was there any evidence of inflammatory change. The proliferative scars showed myxomatous, fatty or hyaline degeneration, while the degenerative ones were the same but without signs of any earlier proliferation. In many instances, the thickened area was poorly defined and appeared as a simple thickening of the normal layers of the valve. Both types, when present, occurred at almost any point on the valves, at the base near the ring, in the midportion, or on or near the free edge. They were found in the valves with and without blood vessels and when vessels were present they appeared to bear no relation to the scars. On many vascularized valves no scars were found. We have interpreted these scars as signs of the

wear and tear of life because we have been unable to discover any evidence of healed or active inflammation in them.*

DISCUSSION

The occurrence of blood vessels in the valves of seventy-four out of eighty-eight hearts represents a much higher incidence than any previously reported. When one considers that all the patients from whom the hearts were obtained gave no clinical evidence of endocarditis, but died of other diseases, the findings seem to indicate that blood vessels occur normally in human heart valves. The occurrence of numerous scars on the valves, however, raises the question of previous valvulitis. Our studies show that in many instances the scars and the vessels were unrelated, and the incidence of vessels in a given valve did not correspond to the incidence of valvulitis in that valve. Moreover, there was no microscopic evidence of active or healed valvulitis in any of the seventy-four hearts. If the vessels are of inflammatory origin in the seventy-four hearts which we have included as normal, it would indicate that about 84 per cent of normal people have had unrecognized endocarditis at some time in their lives. If the vessels are not of inflammatory origin, as our studies suggest, one must accept the fact that blood vessels occur normally in human heart valves.

SUMMARY

1. In one hundred hearts from patients without history or clinical evidence of endocarditis, blood vessels were demonstrated in the valves of eighty-six.

2. Twelve of the hearts showed evidence of active or healed valvulitis on one or more valves.

3. Active or healed valvulitis occurred in the absence of blood vessels, and blood vessels were found in valves without evidence of active or healed valvulitis.

4. Of the eighty-eight hearts without evidence of previous inflammation, blood vessels were found in one or more of the valves in 84 per cent.

5. The incidence of blood vessels in a given heart valve was not in keeping with the incidence of rheumatic valvulitis in that valve.

6. A method of injecting the blood vessels in heart valves is described.

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*A more detailed study is being made on a series of four hundred human hearts in which the blood vessels in the valves have been injected; and will be published soon.

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NOTES ON CARDIAC PAIN AND CORONARY DISEASE

CORRELATION OF OBSERVATIONS MADE DURING LIFE WITH STRUCTURAL CHANGES FOUND AT AUTOPSY IN 476 CASES*†

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THE mechanism by which painful impulses are initiated in the heart is, as yet, but imperfectly understood. There is much evidence in support of the current belief that the most important predisposing cause is relative ischemia of the myocardium.¹ The commonest, though not the sole condition leading to a deficient supply of blood to the heart muscle, is impairment of the coronary circulation. In these notes, an attempt is made to define some of the clinical and pathological features of coronary disease which are associated with cardiac pain and which appear to favor its occurrence. At this time, only certain general statements are made. More detailed study of various aspects of the subject will be reported later.

MATERIAL

The cases were assembled from the files of the Department of Pathology‡ in much the same manner as described in an earlier paper.² The twelve-year period from 1918 to 1929, inclusive, was chosen because the work was begun in 1930 and the clinical records prior to 1918 often failed to contain the information desired. Each protocol indexed under the following headings was examined: arteriosclerosis of the coronary arteries, thrombosis of a coronary artery, infarct of the myocardium, aneurysm of the heart, fibrosis of the myocardium, embolism of a coronary artery, occlusion of the coronary arteries, syphilis of the aorta, stenosis of the orifice of a coronary artery, rheumatic coronary arteritis, rheumatic aortitis and generalized arteriosclerosis. Particularly under this last caption were found numerous cases showing the lesser grades of coronary sclerosis and not included in the diagnostic files as coronary disease. A detailed analysis was made of 476 cases showing lesions in the coronary arteries or the aorta. Both clinical and pathological findings were recorded on special charts. The cases were divided, for purposes of study, into four etiological groups as shown in Table I, namely, arteriosclerosis, syphilis, rheumatic fever, and miscellaneous. The observations

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made during life were correlated with the structural changes noted at autopsy. Cardiac pain was the central point of interest about which the other features were grouped, and only such facts are here presented as bear upon the presence or absence of painful discomfort. Because of the relatively small number of records, the results of the analysis are to be regarded as applying to this particular group of patients and not necessarily as generalizations.

FACTS NOTED

General Observations.—From Table I it is apparent that:

1. Cardiac pain occurred in the presence of a few scattered intimal plaques in the coronary arteries, as well as when many were found. Even calcification of the artery or narrowing of the lumen did not increase the

TABLE I
INCIDENCE OF CARDIAC PAIN IN 476 CASES WITH VARIOUS LESIONS

ETIOLOGICAL GROUP	TOTAL NUMBER OF CASES	PAIN PRESENT (PER CENT)
A. Coronary arteriosclerosis		
1. Few to many plaques	201	20
2. With calcification or stenosis	103	23
3. With arteriosclerotic occlusion	34	44
4. With thrombosis	33	39
B. Syphilitic aortitis		
1. Coronary mouths not involved	14	0
2. Coronary mouths narrowed or occluded	7	86
3. Coronary mouths not involved; coronary sclerosis present	32	22
4. Coronary mouths narrowed or occluded; coronary sclerosis present	11	64
C. Rheumatic fever		
1. Coronary arteritis	3	33
2. Aortitis; no coronary involvement	12	25
3. Aortitis; coronary sclerosis present	16	50
D. Miscellaneous	10	70

incidence. This observation suggests the inference that irritation in the wall of an artery or spasm, or both, may be causative factors. It was only when the vessel was actually occluded, either by the arteriosclerotic process or by thrombosis, that the incidence of pain doubled. Thus, pain was present in but 20 per cent of the cases with coronary sclerosis without occlusion, and in 40 per cent of cases with closure of a branch. In Russia, Kudrin,³ studying 500 cases of coronary sclerosis at autopsy, found narrowing of the lumen in 22 per cent giving a history of anginal attacks and in only 5 per cent of the remainder. Occlusion was noted in 30 per cent of cases with pain and in only 4.6 per cent of those without discomfort. But the conditions which determine the presence or absence of pain in any given instance are not clearly defined.

2. In fourteen cases of simple syphilitic aortitis without coronary involvement, either specific or arteriosclerotic, pain was not noted in a single instance. On the other hand, when the mouths of the coronaries were narrowed or occluded by the syphilitic process, pain occurred in six of seven cases (86 per cent). It may therefore be said that in syphilitic aortitis in the absence of aneurysm, if chest pain is present, there is involvement of the coronary arteries either at their orifices by syphilis, or farther along in their course, by arteriosclerosis. Obviously, these two etiological types of coronary pathology may coexist. It has previously been pointed out that pain is not part of the picture of uncomplicated aortitis;^{1a, 4} but this observation has not been sufficiently stressed.

3. In rheumatic fever, of which thirty-one cases were included in the series, pain occurred in association with either coronary arteritis or rheumatic aortitis. More extensive and detailed microscopic study, as made by Karsner and Bayless,⁵ will perhaps reveal rheumatic coronary lesions in a higher percentage of cases. In the older rheumatic patients, sclerotic lesions in the coronaries increased the likelihood of the occurrence of attacks of pain.

4. Paroxysmal pain referred to the sternum or precardial area, and simulating that observed in the presence of intrinsic coronary pathology, occurred as part of the clinical picture in a variety of conditions. In the ten cases included in a miscellaneous group were instances of cardiac hypertrophy of unknown etiology, with myocardial lesions; pulmonary arteritis; embolism of a coronary artery; adherent pericardium; syphilitic myocarditis; ball thrombus in the left ventricle with aneurysm of the heart; aortic aneurysm compressing the right coronary artery. In some of these cases the coronary blood flow was impaired; in others a few intimal plaques were found in the coronary vessels. This group serves to emphasize the fact that cardiac pain is observed in association with a variety of pathological states.

The Rôle of Aortic Insufficiency.—Of 474 patients, 415 did not have aortic insufficiency; pain was present in this group in 24 per cent. In the 59 cases with aortic insufficiency, pain was noted in 49 per cent. It appears, then, that patients with aortic insufficiency are twice as likely to have pain as those without it. This is probably due to the lowered diastolic pressure in certain instances, with resultant diminution in the amount of coronary blood flow.⁶

On the other hand, the presence of aortic insufficiency without associated coronary lesions does not necessarily induce discomfort. Thus, in four cases of syphilitic aortitis with aortic insufficiency but without coronary pathology, there was no pain.

Arteriosclerosis of the Coronary Arteries.—This group comprised the greatest number of cases—338. The following observations were made:

1. The ages ranged from twenty to eighty-five years, with averages in the various subgroups shown in Table I, from 51 to 65 years. The milder grades of sclerosis were observed in the younger patients.

2. There were twice as many males as females in the series. Yet the incidence of pain was the same in both sexes, i.e., 23 per cent in males and 24 per cent in females. Marked sclerosis was more common in the males in the ratio of 3 to 1.

3. In the total hospital autopsy series, the ratio of white to negro is 11 to 1. In this series it was 12 to 1. But of 137 cases of advanced sclerosis, 133 were in whites and only 4 in blacks. This is a ratio of 34 to 1. The incidence of pain in the two races was, however, the same (Table II).

The infrequency of the anginal syndrome in the colored race has repeatedly been the subject of comment.⁷ One reason for this observation appears to be the fact that advanced sclerosis of the coronary arteries is relatively rare in the negro.

TABLE II

INCIDENCE OF CARDIAC PAIN IN 310 WHITES AND 27 NEGROES IN RELATION TO THE DEGREE OF CORONARY SCLEROSIS

	WHITES		NEGROES	
	TOTAL NUMBER OF CASES	PAIN PRESENT (PER CENT)	TOTAL NUMBER OF CASES	PAIN PRESENT (PER CENT)
Few to many plaques	177	19	23	30
Calcification or stenosis	100	24	3	0
Arteriosclerotic occlusion	33	45	1	0
Total group	310	24	27	26

4. In a previous paper it was pointed out that occupation does not appear to play a significant part in determining those whose coronary arteries are affected by sclerosis.² The largest number of patients with coronary sclerosis was found among foremen and skilled workers, but the figures in different occupational groups did not show wide variations. With respect to the occurrence of pain, however, occupation seems to be of real importance (Table III). The highest incidences were found

TABLE III

INCIDENCE OF CARDIAC PAIN IN RELATION TO OCCUPATION IN 311 CASES OF CORONARY SCLEROSIS

OCCUPATION	TOTAL NUMBER OF CASES	PAIN PRESENT (PER CENT)
Housewives	96	29
Manual laborers	88	28
Clerical workers	38	21
Foremen and skilled workers	50	18
Professional men and executives	39	18

in housewives and manual laborers (29 and 28 per cent, respectively). Clerical workers occupied an intermediate position (21 per cent), whereas foremen and skilled workers, as well as professional men and executives, showed an incidence of only 18 per cent.

A somewhat similar set of observations was made by Kleimann,⁵ working in Aschoff's laboratory in Freiburg. He, too, noted that in the presence of coronary sclerosis those individuals whose daily work called for physical effort were most likely to experience pain. He found an equally high incidence among those whose occupations, in addition to physical exertion, involved emotional stress. In this latter group he specifically mentions physicians.

That the housewives should occupy such a prominent place in our own series is not surprising if account is taken of the fact that the women who occupy beds in the hospital wards almost invariably do their own housework. Scrubbing, washing, and lifting are integral parts of their daily chores. The character of their activities may well be classed as manual labor.

5. Congestive heart failure was present in 154, absent in 184 cases. Pain was frequent in those patients who gave a history of congestive failure (40 per cent); it was relatively uncommon in those who had not had failure (10 per cent). Conversely, in 80 cases with pain, congestive failure was observed in 78 per cent; in 258 cases without pain, congestive failure was noted in only 37 per cent. In short, in a group of patients sick enough to seek relief in a hospital and eventually to die there, pain was four times as frequent in those who had congestive failure as in those whose myocardial function was well preserved. And congestive failure was twice as common in the patients with pain as in those without it. These figures are undoubtedly influenced by the fact that patients with coronary disease rarely seek bed care for pain alone; they enter the hospital because of cardiac insufficiency. Those without pain were largely instances of latent coronary sclerosis discovered at autopsy in subjects who died of conditions not directly related to the cardiovascular system.

6. The presence or absence of hypertension, in the group as a whole, had no effect on the incidence of pain. But of fifty-one males with pain, 48 per cent had hypertension; of twenty-seven females, 74 per cent had hypertension. There is an association between cardiac pain and elevation of the blood pressure in women. This relationship has previously been noted by Eppinger and Levine⁹ who believe that, in females, it may be used as a diagnostic aid in distinguishing pain of cardiac origin from that due to other causes. Although, on the basis of probability, cardiac pain in a woman with normal blood pressure is not due to coronary disease, each individual case must be the subject of special study.

7. Electrocardiograms were taken in 138 cases. Deviations from the normal were found in 120 (87 per cent). The most frequently observed changes were significant T-wave negativity (88 cases); auricular fibrillation (36 cases); ventricular premature beats (33 cases); auriculoventricular block (24 cases) and bundle-branch block (19 cases). Pain was twice as common in the patients with abnormal, as in those with normal, graphic records (44 per cent as against 22 per cent).

8. Cardiac hypertrophy was found in 236 cases (70 per cent). In the patients with hearts of normal weight, 13 per cent had pain; of the group with enlarged hearts, 27 per cent had pain—again a doubled incidence. Furthermore, in the series with hypertrophy the hearts of patients with pain were consistently larger than those without it. The average weights (both sexes) were: with pain, 543 grams; without pain, 505 grams.

9. Fibrosis of the myocardium, gross or microscopic, was present in 204 cases (60 per cent). Pain occurred much more frequently in the presence of fibrosis (31 per cent) than in its absence (12 per cent). In 80 cases with pain, fibrosis was present in 80 per cent; in 257 cases without pain, fibrosis was present in 55 per cent. Kleimann,⁸ to whose paper reference has already been made, observed cardiac pain five times as frequently in patients whose hearts at autopsy showed fibrotic scars as in those whose did not.

Deviations from the normal in the form of the electrocardiogram, cardiac hypertrophy, and fibrosis of the myocardium are all signs of a damaged heart muscle. In the cases under discussion, such damage is the result of impairment of the blood supply.¹⁰ Pain, then, is more likely to be experienced by the person with a damaged myocardium than by one whose heart muscle has not suffered materially from the milder grades of ischemia.

Coronary Thrombosis.—1. Of 33 patients, 2 died in coma within an hour after admission to the hospital, so that no history was obtainable. Of the remaining 31, 12 (39 per cent) had pain with the attack. In a series of 76 cases collected by Davis,¹¹ in Chicago, there was a history of pain in 47 per cent. Certainly pain is present in less than half of the cases which come to autopsy. If the milder forms described by Levy¹² are taken into account, the incidence is probably even lower than that here given. In our experience, those patients who had no symptoms prior to the acute episode were most likely to have no pain associated with it.

The particular artery occluded was not alone responsible for determining the presence or absence of pain; nor did the occurrence of myocardial fibrosis outside the area of infarction seem to play a part.

2. There was only one negro in this series of 33 cases. The relative infrequency of coronary thrombosis in the colored race is probably directly related to the rarity of advanced coronary sclerosis in the black, as previously noted in this paper.

3. Four patients with cardiac aneurysm had no pain associated with the final acute occlusion. As Herrick¹⁵ has pointed out, the area irrigated by the artery in such cases has become comparatively insensitive due to destruction of vessels, nerves, and functioning muscular tissue, so that a painful response to the new obstruction is not experienced. Under these circumstances, dyspnea, sudden weakness, sweating, or pulmonary edema may be the pain equivalent.

SUMMARY

In these notes, an attempt is made to define some of the clinical and pathological features of coronary disease which are associated with cardiac pain and appear to favor its occurrence. Among the factors considered are the etiology of the coronary lesions; their extent, with particular reference to stenosis or occlusion of an artery or its orifice; the influence of sex, race, and occupation; the relationship between pain and congestive failure; the association with hypertension; the effect of damage to the heart muscle, as shown by cardiac hypertrophy, fibrosis of the myocardium and changes in the form of the electrocardiogram; and the rôle of aortic insufficiency.

All of the conditions which determine the presence or absence of pain in any given instance are not known. But a number of the factors cited are clearly concerned in predisposing to painful discomfort.

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ELECTROCARDIOGRAMS DERIVED FROM ELEVEN FETUSES THROUGH THE MEDIUM OF DIRECT LEADS*

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DURING the course of a routine study of the cardiac mechanisms of premature and full-term infants, we were fortunate in securing a fetus of twelve and one-half weeks' gestation a few minutes after its delivery by hysterotomy. Knowing that electrocardiograms had been obtained from the embryo chick, we endeavored to obtain electrocardiographic curves from this human embryo. In this attempt we were successful. Six months later, on April 14, 1934, the results of this study were reported at a meeting of the Biological Society of the University of Pittsburgh. At that time a search of the literature failed to show that previous attempts had been made to secure electrocardiograms from human fetuses through the medium of direct leads.

Staff positions in a hospital under university control affording approximately 2,400 births annually have provided us with material for a continuance of our study. We have up to this time electrocardiograms from eleven fetuses, eighteen premature infants, and eighty full-term infants. The present report is a preliminary one and will be confined to our observations upon members of the first group. During the course of this communication, we will use the term fetus as applied to those members of the entire group in which the period of gestation varied from $9\frac{1}{2}$ to 25 weeks, estimations of age being based upon Streeter's *Charts of the Human Embryo*.¹

Of our eleven fetuses, seven were obtained by hysterotomy. With one exception these had been kept totally immersed in warm Tyrode's solution from time of delivery. They were removed from this solution on arrival at heart station. There they were allowed to cool to room temperature. The fetuses which had been delivered spontaneously were not immersed. The placenta was detached from only one of the fetuses which had been removed by hysterotomy. From the others it had been separated at time of delivery. Six of the hysterotomized women had been delivered under spinal anesthesia, one under ether. The mothers who had delivered spontaneously received morphine sulphate only. Neither type of anesthetic or analgesic administered to mothers nor separation from placenta previous to total

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immersion or non-immersion appeared to influence the pattern of the electrocardiograms or the periods of time over which deflections could be recorded.

In all instances a stationary electrocardiograph was employed without resort to amplification. Ordinary copper wire was used for electrodes, with standard hook-up. The fourth lead was obtained in accordance with the technic of Wolferth and Wood.² Apparently our difficulties in maintaining accurate standardization throughout the longer periods of observation have had little or no effect upon the results obtained.

We believe that we are justified in reporting the details of our findings inasmuch as we are able to discover at this time but one reference to an electrocardiogram derived from fetus through the medium of direct leads. In October, 1934, or one year after our first electrocardiogram had been obtained, Dr. Mary Easby³ published an electrocardiogram taken from a fetus of four and a half months' gestation. An attempt to obtain limb leads was successful only in regard to Lead II. Chest leads were recorded, but no statement is made as to which electrode was employed anteriorly.

We are aware, of course, that several reports have been made of galvanometric curves obtained from the fetus in utero.^{4, 5} Such studies are of interest but are not strictly comparable with those based upon results obtained through the direct application of the standard technic.

Our observations rest upon analysis of three standard limb leads obtained from all eleven fetuses as well as of fourth lead curves from five of them. Serial electrocardiograms were obtained from four fetuses. In one instance, observation continued to the point at which deflections ceased to appear. In the others, deflections could still be recorded at the time when the subjects were removed from the heart station.

Table I gives a tabulation of our readings.

DISCUSSION

To us, the most interesting outcome of our study was our ability to prove that electrocardiograms can be readily obtained from fetuses by means of the usual technic as applied to all four of the standard leads. We had but one failure in spite of the fact that most of our subjects had been totally immersed for periods varying from seven to thirty minutes before they were available to us.

The persistence of deflections over relatively long periods of time is worthy of comment. In three of the subjects, deflections were still obtainable at periods of 35 minutes, 55 minutes, and 205 minutes after their delivery by hysterotomy. In a fourth fetus deflections ceased

210 minutes after its spontaneous delivery. It is possible that such deflections may represent a passage of the excitation wave without contraction of heart muscle.⁶

The amplitude of the deflections which we recorded in our series was usually somewhat lower than that derived from adult hearts; but occasional exceptions occurred in derivations from limbs while the T-wave as derived from chest lead showed a marked excursion from the isoelectric line.

The initial rate of cycles varied widely: the highest was 100; the lowest, 35. It will be obvious that in all instances, these rates are lower than the audible rates recorded from fetuses in utero. In all of our subjects from whom serial electrocardiograms were obtained, progressive slowing of rate was recorded. Thus, in one fetus the rate fell from 86 to 42 over a period of thirty-five minutes. It is probable that gradual cooling of the fetuses was partly responsible for this slowing of rate.

Left axis deviation was not present in any of the electrocardiograms. In five instances, right predominance was present; in six, no dominance was demonstrated. It is to be noted that in one of the cases in which dominance was not discernible in the first electrocardiogram, a definite right deviation appeared thirty-five minutes later.

The sinus node was dominant in all of our initial electrocardiograms. Slight sinus arrhythmia was present in four. In one subject the A-V node became dominant a short time before deflections ceased.

P₁ was negative in one instance. P₄ was invariably negative where S-A node was dominant. In the one case in which nodal rhythm was established, the previously negative P₄ became positive.

The comparison of the conduction time in the human adult heart with that of the human fetus shows the fetal conduction time to be only slightly shorter. This, in view of the relatively enormous difference in the size of the two hearts, indicates that the excitation wave in the human fetal heart is much slower than the excitation wave in the human adult heart. Studies of the conduction mechanism in the chick embryo and the adult hen have shown this same relationship to be present. An observation in the literature, which is of interest in the consideration of the conduction time, would indicate that the relative size of the heart has but little influence on the speed of the excitation wave. Thus a small bat had a conduction time of 0.03 as compared with a conduction time of 0.30 in an elephant, which was 400,000 times the weight of the bat; a ratio of 10 to 1 in the conduction time as compared with 400,000 to 1 in weight.⁷

Q-waves were not recognized in any of our standard leads.

The primary complexes were monophasic in all limb leads in two of our subjects: it was diphasic in all limb leads in two; it occurred

TABLE I
TABULATION OF READINGS OF ELECTROCARDIOGRAMS DERIVED FROM HUMAN FETUSES THROUGH THE MEDIUM OF DIRECT LEADS

	NO. 1 9½ WK. A	NO. 2 11½ WK. A	NO. 3 12½ WK. A	NO. 4 13 WK. A	NO. 5 14 WK. A	NO. 6 14 WK. A	NO. 7 22 WK. A	NO. 8 18 WK. B	NO. 9 18 WK. B	NO. 10 22 WK. B	NO. 11 25 WK. B
Rate	90-50	48	80	92-80	90	90 80 60	86-42	45-22	35-29	60	100-92
Rhythm	Irrég. Sinus Iso.	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Irrég. Sinus	Irrég. Sinus	Sinus	Irrég. Sinus
P-I	Iso.	Iso.	Neg. M.V. 1+	Pos. M.V. 1+	Pos. M.V. 1+	Iso.	Pos. M.V. 1+	Pos. M.V. 2	Pos. M.V. 2+	Pos. M.V. 1+	Pos. M.V. 1
P-II	Invert Iso. Pos.	Pos. M.V. 2+	Iso.	Pos. M.V. 1+	Pos. M.V. 1+	Pos. M.V. 2+	Pos. M.V. 1+	Pos. M.V. 2+	Pos. M.V. 1+	Pos. M.V. 3	Pos. M.V. 1+
P-III	Iso.	Iso.	Iso.	Iso.	Iso.	Pos. M.V. 1+	Neg. M.V. 1+	Pos. M.V. 2	Iso.	Pos. M.V. 1+	Pos. M.V. 1+
P-IV		Invert M.V. 1+					Invert M.V. 2+		Invert M.V. 2+	Invert M.V. 2	Invert M.V. 1
Axis deviation	No	Right	No	Right	No	Right	No	Right	No	Right	No
T-I	Iso.	Iso.	Neg. M.V. 1+	Pos. M.V. 1+	Pos. M.V. 1+	Pos. M.V. 2+	Pos. M.V. 1+	Pos. M.V. 2	Iso.	Pos. M.V. 2	Pos. M.V. 1+
T-II	Diph.	Iso.	Neg. M.V. 1+	Pos. M.V. 1+	Pos. M.V. 1+	Pos. M.V. 2+	Pos. M.V. 1+	Pos. M.V. 2	Iso.	Pos. M.V. 1+	Pos. M.V. 1

TABLE I—CONT'D

[illegible]

in one or more limb leads in seven. In Lead IV the primary complex was invariably diphasic.

The S-T interval was isoelectric in all limb leads. In Lead IV it was isoelectric, or nearly so, in one; the take-off was slightly high in four.

In one of our subjects T_1 was negative. In three others T_1 was isoelectric. T_2 was isoelectric in two; negative in one and diphasic in one. T_4 was positive in four; in one instance T_4 was negative as in the normal adult. (In Figs. 1 and 2 this difference in potential is shown.) We are unable to account for this variation. It is of some interest that the subject from which the negative T_4 was derived was the oldest fetus of the group and that this fetus had made slight

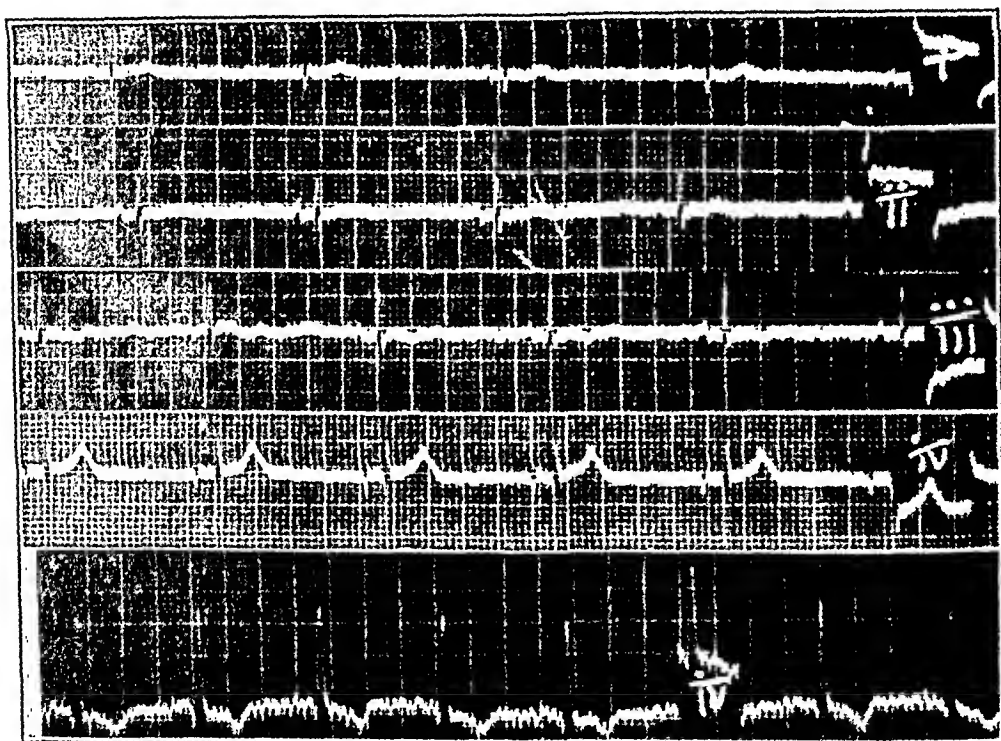


Fig. 1.—Fetus 10 with control adult Lead IV, strip E. In strip D a positive T_4 is shown, a confirmation which was present in four of the five chest leads obtained (Fetuses 2, 7, 9, and 10).

gasping movements at intervals of one to one and one-half minutes. Of the fetuses from which a positive T had been derived, only one had shown respiratory movements and these occurred at relatively longer intervals. The question arises as to whether a relatively high density of fetal lung may influence the potential of T as derived from anteroposterior chest lead. It is possible that our investigations now in progress may throw further light upon the potential of T_4 as derived from a fetus.

Serial electrocardiograms of the single member of our group in which we were able to continue our observations until deflections

ceased showed the following variations; the progressive slowing noted in the course of all of our serial studies together with periods of asystole, the appearance of a single ectopic beat of ventricular origin, shifting of pacemaker to A-V node, and the gradual widening of the primary ventricular complexes. A similar sequence of events had

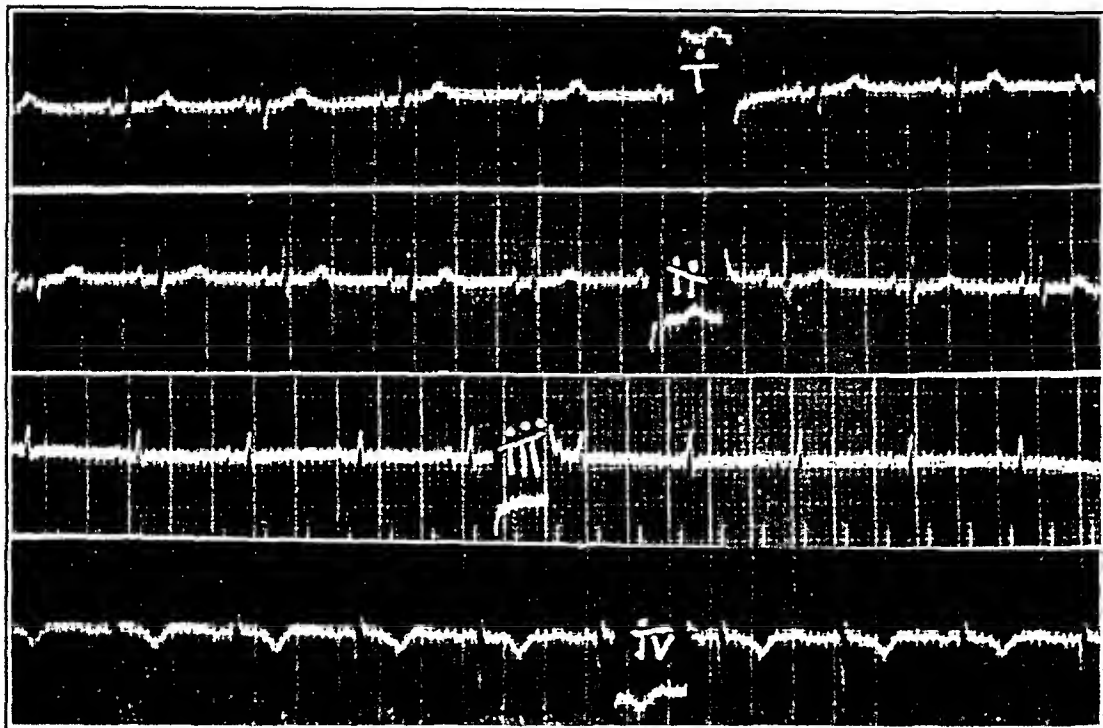


Fig. 2.—In strip *D* is shown the only negative T_1 which occurred in the series (Fetus 11, age estimated at twenty-five weeks).

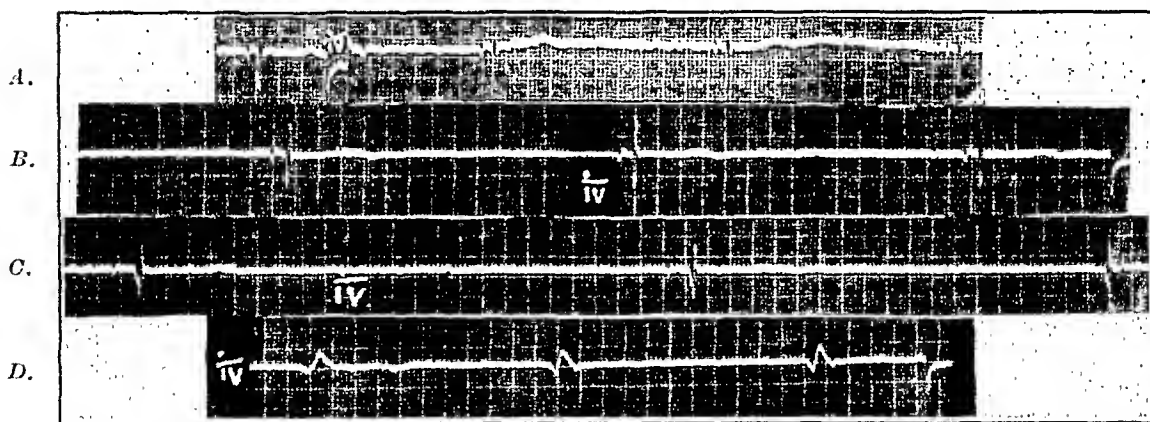


Fig. 3.—Four strips of Lead IV; an interval of about three hours elapsed in securing of records *A* and *D*. The third complex in strip *C* is under dominance A-V node. Strip *D* was secured a few minutes before deflection ceased (Fetus 9, age estimated at eighteen weeks).

been recorded by Hanson, Purks, and Anderson⁶ during the course of electrocardiographic studies of the dying hearts of human adults. In their series of twenty-five patients these authors noted that the period elapsing from clinical death to final deflections averages five minutes; the longest period was thirty-five minutes. In their cases

rapid heart action of sinus origin was followed by progressive slowing; the pacemaker was frequently migratory and shifted between the sinus and the A-V nodes; short periods of asystole occurred frequently; heart block and extrasystoles were common; ventricular fibrillation was a frequent terminal event.

Our case adds nothing to the phenomena previously observed in the dying adult heart, except that in our fetuses cardiac activity persisted six times as long as in any of the adult cases of Hanson and his associates. Our series of fetuses is not large enough to permit of generalization, but it would seem probable that, since embryonic tissues are very resistant to asphyxial conditions, activity in dying fetal hearts should persist longer than in the fully developed subject.

CONCLUSIONS

1. Through the use of standard equipment and the employment of the standard technique, satisfactory electrocardiograms may be directly derived from fetuses at very early periods of gestation.

2. In all three limb leads and in standard chest leads, the major deflections which are present in the electrocardiograms of the adult appear.

3. Minor variations from the pattern of the normal electrocardiogram of the adult have appeared in members of our series.

For cooperation in collecting our material and for helpful suggestions as to the analysis of our results, grateful acknowledgment is made to the Obstetrical Staff of the Elizabeth Steel Magee Hospital and to Dr. Davenport Hooker, Dr. C. C. Guthrie, and Dr. A. B. Fuller.

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A STUDY OF LEAD IV OF THE ELECTROCARDIOGRAM IN CHILDREN WITH ESPECIAL REFERENCE TO THE DIRECTION OF EXCURSION OF THE T-WAVE*

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THE chief criteria which have been developed for the normal Lead IV of the electrocardiogram of Wolferth and Wood¹ by these and later investigators^{2, 3, 4, 5} are: (1) smoothly rapidly described Q, R, and S deflections, without slurring or notching; (2) a definite Q-wave of over 2 mm. in amplitude; (3) an S-T interval without depression greater than 2 mm.; (4) a T-wave negatively described, with a depth greater than 2 mm.

These criteria hold equally for the anteroposterior placement of the electrodes or for the placement of the first electrode over the second to fourth left sternocostal junctions and the second electrode over the left leg. Some variation in form of the electrocardiogram has been observed by Hoffman and De Long⁶ on placement of the respective electrodes in various positions on the anterior and posterior chest walls, but for the standard lead above described no one has reported any striking variations in normal humans from the recognized criteria.

It has been our observation that such variation occurs in at least one characteristic and this fact may warrant some alteration of these standards of normality.

Electrocardiograms were made of fifty normal children who varied in ages from one month to sixteen years. These included the three standard leads, and a fourth lead with the first electrode (right arm lead) over the left second, third, and fourth sternocostal junctions and the second electrode (left arm lead) placed over the sixth to eighth thoracic spines on the posterior chest wall.

In contrast to this series, sixty-six records were selected from the general electrocardiographic files of patients with no proved heart disease and with the standard three leads showing no recognized abnormality other than deviation of the electrical axis.

The summary of the data on these two groups is presented in Table I and Table II. It will be seen that the direction and depth of the P-waves, the QRS complex components, the S-T interval, and the direction and extent of excursion of the T-waves have been entered in Table I; only the T-waves are shown in Table II.

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TABLE I
AN ANALYSIS OF LEAD IV IN 50 NORMAL CHILDREN

NO. OF PATIENTS	AGES IN YR.	SIX			P			R AV. DEPTH MM.	R AV. HEIGHT MM.	S		T							S-T					
		RT./NO.	NORM./NO.	LT./NO.	+/NO.	ISO./NO.	DIPH./NO.			-/NO.	NO.	+	NO.	ISO.	NO.	DIPH.	AV. DEPTH	NO.	+	NO.	DEPRESSION	AV. DEPTH MM.		
10	51-01	4	4	10	1	13	3	4	7.8	4.1	5.4	3	7	8	1	3	0	1.5	0	1	0	1	0	1.0
10	01-5	4	5	10	1	13	3	4	8.3	11.8	8.6	4	6	7	1	4	1	3	0	1	0	1	0	1.0
10	2-5	3	3	0	1	4	1	1	8.2	5.8	5.9	1	4	4	0	4	0	3	0	0	0	1	0	1.0
10	1-0	2	3	0	1	4	1	1	7.9	4.9	4.9	1	4	5	0	3	0	1	0	0	0	1	0	1.0

Analysis of the tables makes it clear that there is one notable difference between the two groups. The electrocardiographic findings in both groups, with one important exception, correspond with the accepted values of normal. This exception consists of a remarkably high incidence of upright T_4 -waves in the tracings of the group of children (Table I). The records of thirty-two of these normal children showed frankly upright T_4 -waves. There were fourteen records in which an isoelectric T_4 was present, and two in which T_4 was diphasic. Finally, there were only two subjects (aged fourteen and one-half and fifteen years) in this entire group whose records showed an inversion of T_4 .

TABLE II

T_4 -WAVE FINDINGS IN 66 ADULTS WITHOUT CARDIAC DISEASE AND WITH NORMAL ELECTROCARDIOGRAPHIC FINDINGS IN LEADS I, II, AND III

T_4 -WAVE FINDINGS	NO. OF CASES	PERCENTAGE OF TOTAL
Inverted	54 (Average depth 2.7 mm.)	80
Isoelectric	6	9
Diphasic	4 (Average depth 2.8 mm.) (Average height 1.5 mm.)	6
Upright	3 (Average height 1.1 mm.)	5

Among the children's records, there were twenty-three instances of right axis deviation, three instances of left axis deviation, and twenty-three in which the electrical axis was normal. No relationship between the direction of the electrical axis and the direction of excursion of T_4 could be detected. With the exception of the T_4 -wave findings, all other measurements of the Lead IV tracings (and of the conventional three leads as well) were within the accepted normal limits.

In contradistinction to the above, examination of Table II, which summarizes the findings in sixty-six adults, shows that in fifty-three of the cases (80.3 per cent) a characteristic "normal" inversion of T_4 was present. In fact, only three of the sixty-six adults showed upright T-waves in Lead IV. Of these three, one was a sixteen-year-old girl who was quite small. The two remaining examples of an upright T_4 consisted of minimal upright deflections, each being less than 1 mm. in height. There were six examples of an isoelectric T_4 and four cases in which the T_4 was diphasic. The diphasic T_4 -waves which were encountered averaged 2.8 mm. in downward and only 1.5 mm. in upward excursion. This type of diphasic T-wave in Lead IV is not considered abnormal.^{3, 4, 5} Generally speaking, therefore, the findings in our adult cases were quite consistent with the established values of normal.

DISCUSSION

These considerations make it plain that an upright T_4 -wave is extremely uncommon in the electrocardiograms of adults without cardiac disease, and confirm the accepted belief that, when present, it constitutes an abnormal finding during adult life in the absence of digitalization.⁷ In normal children, on the other hand, an upright T_4 occurs with such regularity that it must be considered to be a normal curve, and in no sense can it be taken to indicate cardiac disease. Diphasic and isoelectric T_4 -waves in the electrocardiograms of children are without diagnostic significance and apparently represent transitional forms between positive and negative T_4 -waves—neither of which are abnormal in childhood.

SUMMARY

Electrocardiograms were made on a group of fifty normal children, and particular attention was paid to the character of the T-wave in Lead IV. A control group of tracings was made from sixty-six adults who had no demonstrable heart disease and in whom the electrocardiograms were within normal limits.

Sixty-four per cent of the tracings of the fifty normal children showed an upright T_4 -wave; 32 per cent exhibited a diphasic or an isoelectric T_4 , and in only 4 per cent of the cases was the T_4 inverted. No relationship between the direction of the electrical axis and that of the T_4 -wave was discoverable.

The inverted T_4 , normal in adult life, is of rare occurrence in the electrocardiograms of normal children, while the upright excursion of T_4 in the electrocardiogram of a child is a normal phenomenon.

We are indebted to Miss Jane Wasserman for technical assistance.

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THE PHARMACOLOGICAL AND THERAPEUTIC EFFECTS OF CERTAIN CHOLINE COMPOUNDS

RESULTS IN THE TREATMENT OF HYPERTENSION, ARTHRITIS, ORGANIC
OCCLUSIVE VASCULAR DISEASE, RAYNAUD'S DISEASE,
SCLERODERMA, AND VARICOSE ULCERS*†

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IT IS our purpose not to review the vast literature covering the choline compounds but rather to discuss certain findings from our own experience, based on three years of study and experimentation with certain choline compounds, and over two thousand treatments, using the technique of iontophoresis, previously described by one of us (Kovacs).¹ Our interest has been concerned chiefly with the improvement of local circulation, and, for that reason, the local induction of the drugs by galvanic current seemed worthy of careful study. That these drugs are readily absorbed by this method has been demonstrated beyond a doubt by the fact that all of the general reactions reported resulting from other methods of administration (e.g., subcutaneous, oral, intravenous) have been duplicated innumerable times under our observation by the use of iontophoresis.

A severe reaction resulting from meclocholyl iontophoresis might be characterized by the following: (a) a marked flush extending over the face, chest and upper abdomen; (b) increase in pulse rate; (c) a deeper, slower respiration cycle; (d) a marked drop in blood pressure (which has been so profound on several occasions that it was necessary to terminate the experiment with atropine); (e) marked salivation (in one instance as much as 140 c.c. of saliva was collected in 20 minutes); (f) marked lachrymation; (g) profuse diaphoresis; (h) increased intestinal peristalsis with abdominal griping and occasional immediate defecation; (i) occasional substernal pressure; (j) diuresis, to a varying degree; (k) changes in the electrocardiogram resulting in temporary inversion of the T-waves in one or more leads; (l) slight cyanosis at the tips of the extremities, with a drop in surface temperature, which usually rises above original level in from one to six hours; and (m) immediate cessation of effects following the injection of atropine.

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TABLE I
EFFECT OF CHOLINE COMPOUNDS ON BASAL METABOLIC RATES

The variations in the control readings for a given patient may be in part explained by certain other factors, such as discomfort due to superficial skin ulcers present during several experiments or restless nights preceding several experiments

READINGS DURING IONTOPHORESIS TREATMENT						
PATIENT C		PATIENT L		PATIENT R		
I Control 1% mech. ionto. 2 hr. later		-5 -6	I Control 1% mech. ionto. 1 1/4 hr. later	-11 -15	I Control 1 hr. later, potato chips and Sanka 1 1/2 hr. later, doryl (1:2,000) ionto. 2 1/2 hr. later	+4 +1
II Control 200 mg. mech. orally 2 hr. later		-8 -10	II Control After restless night	-9		
III Control 500 mg. mech. orally 2 1/4 hr. later		-10 -7	III Control After restful night	-21	II Control 0.1 gm. acetylcholine chloride subent. 1 3/4 hr. later.	-4 -7
IV Control 1,000 mg. mech. orally 2 1/2 hr. later		-10 ± 0	Mech. 1,100 mg. orally (vomited small amount?) After 2 hr.	-16	III Control 1% mech. ionto. 2 hr. later	-5 -11
V Control 0.1 gm. acetylcholine chloride subcutaneously 1 3/4 hr. later		-12 -6	IV Control 0.1 gm. acetylcholine chloride subent. 1 1/2 hr. later.	-19 -20		
VI Control Control—no med. 3 3/4 hr. later		-9 -6	V Control Doryl (1:2,000 sol.) ionto. 1 1/4 hr. later	-19 -15	IV Control 1% acetylcholine chloride, ionto. 2 1/4 hr. later	-13 -7
VII Control 1,000 mg. acetylcholine chloride orally 2 1/4 hr. later		-6 -1				
VIII Control 2,000 mg. acetylcholine chloride orally 2 hr. later		-12 -4	PATIENT M I Control 1% mech. ionto. 1 hr. later	-13 -12	V Control 1,000 mg. mech. orally 1 1/2 hr. later	-4 -8
IX Control 1% acetylcholine chloride, ionto. 2 1/2 hr. later		-10 -6	II Control 1,000 mg. mech. orally 2 hr. later	-15 -9	VI Control 1,500 mg. acetylcholine orally 1 1/2 hr. later	-11 -7
X Control Doryl (1:2,000 sol.) ionto. 2 hr. later		-15 -9				
Mech. Ionto. \rightarrow Mecholyl Iontophoresis						
						+16 +17 +22 +19

In addition, there is a characteristic local reaction, directly under the site of application of the drug. This consists of (a) a feeling of prickling followed by warmth during the treatment; (b) the appearance of goose-flesh immediately after removal of the positive pole; (c) a local blush of the skin; (d) sweating of the skin, which may continue from six to eight hours; and (e) an elevation in surface temperature during treatment, followed by a drop during profuse sweating (with accompanying evaporation), and a rise above the former level in from one-half to five hours. Similar reactions have been produced using carbaminoyl-cholinechloride (doryl) and ethyl- β -methylecholine chloride (weaker) by iontophoresis.*

It should be noted that this description might well be applied to a severe reaction following the use of a slight overdose (subcutaneously or orally) of any of a number of the choline derivatives (mecholy, doryl, acetylcholine [weaker], pacyl and others). Such reactions have been discussed in detail by Starr and his coworkers,^{2, 3} Page,⁴ Abbott⁵ and others.

It would seem that the range of individual susceptibility to these drugs, regardless of the method of administration, varies markedly, and also that the same individual at different times may show a difference in reaction. Certain individuals who scarcely reacted to iontophoresis during the first treatments later manifested all of the local and general reactions above described. In our previous work, we used a 1 per cent solution of acetyl- β -methylecholine chloride with 20 to 30 milliamperes of current for 20 to 35 minutes. (For details, see Kovacs' reports.^{1, 6}) Today, we are using a 0.5 per cent solution and it is possible to get essentially identical reactions with far higher dilutions.

Last year, we noted a marked rise in the basal metabolic rates in two patients. They were controlled as follows: A normal basal metabolism test was taken, using a Benedict-Roth machine. In one case, a reading of 0 was obtained. Normal saline solution was then used for an iontophoresis treatment. The metabolism showed a rise to plus 4 per cent. Mecholy solution was next used for the iontophoresis, and another reading was made near the end of the treatment. This time the reading was plus 55 per cent. The second patient showed a similar increase to 31 per cent.

This year, Dr. Cameron Bailey has worked on the problem with us, using a more accurate, open-circuit method of metabolic determination. We have used a group of individuals, with a variety of drugs and methods of administration for each patient, in order to attempt comparative studies. The results clearly show that the basal metabolic rate is not profoundly disturbed by the use of the choline in

*The choline compounds used in these studies were supplied through the kindness of Merck & Company, Inc.

the dosages and methods indicated. Each experiment was performed on a separate day, and the control was taken under usual basal conditions.

A possible explanation of the high readings obtained in the earlier experiment is that the closed circuit method does not permit ex- pectoration and measures the total oxygen utilized. In order to take care of the saliva, the patient continually swallowed, and probably swallowed large amounts of, O_2 . With a tube in the mouth and the nose clipped shut, the act of swallowing is extremely difficult and can be accomplished only with a considerable expenditure of energy and some anxiety, both of which raise the rate of heat production. These sources of error are not present in the open-circuit method. Starr and his coworkers² report no rise in four cases studied (two with the Benedict-Roth apparatus) after 200 to 400 mg. of mecholyl has been orally administered, but such a dosage would probably be too small to produce a metabolic increase in view of the fact that 1,000 to 2,000 mg. doses were necessary to produce a generalized reaction. Inasmuch as many of our determinations were made while the patients were experiencing marked general reactions, we must conclude that no consistent change in basal metabolic rate results from the use of the choline compounds in the dosages indicated. The

TABLE II

EFFECTS OF DORYL ON BLOOD PRESSURE

Carbaminoyl-cholinechloride (doryl) (1:2,000 solution) by iontophoresis. Treatment twenty minutes at 20 milliamperes.

EXPERIMENT I	EXPERIMENT II	EXPERIMENT III	EXPERIMENT IV
CONTROL 210	CONTROL 160	CONTROL 168	CONTROL 190
STABILIZED 110	STABILIZED 90	STABILIZED 118	STABILIZED 130
3:05 P.M.—Treatment started	11:15 A.M. 160/90	11:50 A.M.—Treatment begun	Treatment, 20 milliamperes, 20 min.
Doryl (1:1,000 sol.) 20 milliamperes	Treatment begun	11:50 A.M. 178/130	10 min. after treatment 154/105
	11:20 A.M. 150/100	12:00 NOON 182/130	
3:09 140/60	11:23 150/100	12:03 P.M. 172/130	
3:10 135/60	11:25 140/90	12:08 172/130	
3:14 110/60	11:30 150/100	12:12 152/110	
Severe general symptoms. Treatment stopped	Treatment ended	Treatment stopped	
	11:35 150/100	12:17 120/108	
	11:40 150/110		
	11:45 150/110		
3:20 140/80	11:50 130/110		
3:25 140/80	11:55 120/110		
3:30 140/80	12:05 P.M. 150/110		
3:45 150/90	12:15 150/110		
4:15 140/90			
4:30 140/90			
21 hr. after treatment 148/90			
92 hr. after treatment 170/86			

marked increase in glandular activity, which is evidenced by the salivation, sweating, etc., and which reaches the peak of activity during the treatment and decreases sharply when the current is turned off, may explain the slight rises noted when the basal metabolism was taken during the treatment.

That the choline compounds lower the blood pressure has been widely recognized. The severity of this action varies from a negligible effect, with a small dosage of acetylcholine, to a very profound effect, with mecholyl⁴ or doryl. By using doryl (1:2,000) iontophoresis, we have been able to produce marked drops in pressure, but, like all other reductions following the use of choline compounds, in our experience, these have been very transient. In not one of the more than two hundred patients who were treated with drugs of this group for varying lengths of time up to two years, have we observed a maintained lowering of either the systolic or the diastolic blood pressures. After taking 1 gm. of acetylcholine each day orally for seven days, one patient's blood pressure had even risen slightly from 160/110 to 168/110, although a drop in pressure followed several of the individual doses.

THERAPEUTIC EFFECTS

Although Hunt and Taveau^{7, 8, 9} by 1911 published studies of seventy-nine homologous or analogous compounds and pointed out that some of these, such as acetyl- β -methylcholine (then believed to be the alpha compound), might well have clinical value, but few choline compounds have been thoroughly investigated as to their possible therapeutic effects. Of these, acetylcholine chloride has been the most exhaustively studied, largely as a result of the stimulation of the work of Villaret and Justin-Besancon.^{10-19, 20} Its value has been reported in a very wide range of conditions, including hypertension,²¹ arteriosclerosis,²¹ hemiplegia,²²⁻²⁴ and cerebral artery spasm,²⁵ epilepsy,^{26, 27, 28} peripheral vascular disease,^{29, 30} varicose ulcers,³¹ angina pectoris,³² ophthalmological problems,³³⁻³⁹ ozena,⁴⁰ paralytic ileus,^{41, 42} hypochlorhydria and hyperchlorhydria,^{43, 44} acrodynia,⁴⁵ tuberculous sweats,¹⁴ and many other conditions.

Our experience and the experiences of many other American workers have been somewhat disappointing with the use of this drug. At present we use it only when we desire to obtain some vasodilatation and when, for some reason, we cannot use one of the stronger and more stable choline compounds.

Starr³ has demonstrated the use of mecholyl in the treatment of paroxysmal tachycardia, and we believe that it has been a favorable influence in a few instances in our experience. He also indicated that it might be useful in certain patients with peripheral vascular disease.

We intend to report briefly our therapeutic results following the use of certain of these drugs:

Arthritis.—Kovacs^{1, 6, 46} reported, in a preliminary way during 1934, on the effects of mecholyl iontophoresis in chronic arthritis. While he did not claim that its action was in any way a curative one, he reported an encouraging percentage of cases with improvement, as judged by reduction in pain, swelling, stiffness, and general evidences of inflammation. To date, 117 patients have been treated for from two weeks to two years, with an average of two treatments per week, with the following results: Although a few have returned to a completely normal state during this period, we do not feel that any of these patients have been cured by this treatment. Forty-four of these patients have had osteoarthritis; of these, 31 have reported definite improvement, while 13 have noticed no improvement; 73 of these patients have had rheumatoid arthritis, and, of this group, 50 have claimed improvement and 23 no improvement. In the groups reported improved are those experiencing temporary improvement. Symptomatic improvement is always difficult to estimate; and, when we consider (1) the psychological effect of an elaborate technical procedure, (2) the fact that certain of these patients relapsed to their former state during treatment, and (3) the fact that only a small group retained their improvement after treatments were stopped, we must revalue these encouraging figures. There were certain individuals in both groups who apparently responded remarkably, but we have frequently seen arthritic patients with sudden remissions, regardless of the therapy used at the time. This, then, must be considered a palliative treatment, useful in chronic arthritis, especially of the rheumatoid type, where other methods of physiotherapy directed at the relief of local conditions frequently fail.

Peripheral Vascular Disease: Arteriosclerosis, Thromboangiitis Obliterans, Emboli.—In our experience, patients suffering from organic occlusion of the major vessels without an appreciable factor of spasm (such as arteriosclerosis, old embolic thrombosis, and thromboangiitis obliterans) have failed to respond satisfactorily to any form of choline compound therapy thus far tried. A few instances in which a factor of spasm was also present, in either the major or collateral circulation, apparently responded with the healing of old ulcerations or with an increased exercise period before claudication.

Raynaud's Disease, Scleroderma, Ulcers.—In contrast, we have had strikingly good results in the treatment of Raynaud's disease. Twelve patients treated throughout last winter reported marked improvement: increased warmth, improved color of hands and feet, and a decrease in frequency and severity of the attacks. Four of these patients had severely painful ulcerations, all of which healed completely. In two instances these ulcers were of more than three months' duration and had been steadily increasing in size. One was

complicated by an advanced degree of scleroderma. All four had been considered as candidates for ganglionectomy.

Six of these patients had complicating scleroderma which involved the hands and, in two instances, was widely distributed over the body. Even in these cases the Raynaud syndrome improved definitely. Five of these patients and one with scleroderma of the hands but without the Raynaud syndrome showed improvement as evidenced by a moderate loosening of their skin, which allowed freer motion. In a study of three cases, the capillaries of the fingers became clearly visible to the point where the blood flow could be seen, whereas before treatment it had been impossible to identify the capillaries definitely. One patient with scleroderma became steadily worse during treatment.

This series was treated with local iontophoresis applied to the hands or feet as indicated. The average number of treatments was three a week, and the number was decreased as the improvement permitted. Practically all of these were ambulatory patients. Our estimation of improvement was based on their reactions during the past winter; such observations would be valueless in the spring or summer months.

Two of this group were males. They were the only users of tobacco but discontinued its use at the onset of treatment.

Varicose and Other Ulcers.—In 1930 Dainow³¹ reported the healing of twenty-nine cases of varicose ulcers of a series of thirty, by the use of acetylcholine injections (0.1 gm. daily) in addition to the usual treatment of rest in bed and wet dressings or ointments. No ulcer required longer than six weeks to heal (except the one failure). Of 199 cases previously treated in the same way without acetylcholine, 31 per cent failed to heal and forty-nine of the ulcers which healed required more than six weeks.

Because we believed that the local treatment with iontophoresis, using mecholyl, might be even more effective, we began to use it in the treatment of varicose ulcers in October, 1934. We wish to report preliminary findings herewith.

Conditions of experiment were: (1) only patients who had long-standing ulcers and who had not had varicose vein injections or whose ulcers had not responded to injection treatment were accepted; (2) no patient received injections during the course of the experiment; (3) no patients were hospitalized or made to refrain from their daily duties, which, in some cases, included washing, ironing, and even chopping wood; (4) no other form of treatment was used (plain vaseline was permitted during the first few days of treatment if it made the patient more comfortable); (5) mecholyl iontophoresis, using 0.5 per cent solution for twenty to thirty minutes at 20 milliamperes, was given two to three times a week. Several received daily

treatments at first. For each treatment, the asbestos cloth, saturated in the solution, was applied over the foot and leg as high as the knee, but not covering the ulcerated area, until a firm scab had formed over it; after this, the application was also made directly over the healed area. (The electrodes were never applied over the affected area.)

CASE REPORTS

CASE 1.—S. N., male, aged fifty-five years, suffered from a varicose ulcer of twelve years' duration and had had a great variety of treatments without effect. Examination: Right leg, lower third, showed an inflamed, edematous, indurated area, 9 cm. \times 4 cm., in the center of which was a deep, punched-out ulcer, 1.8 cm. \times 1.8 cm. Greatly dilated, tortuous veins were noted, extending up above the knee. Mecholyt iontophoresis was given three times weekly. Definite evidence of healing was noted after the fourth treatment. The ulcer was healed after the sixteenth treatment, at which time he was referred for varicose vein injections.

CASE 2.—B. K., female, aged sixty-two years, had varicose ulcers of recurrent duration over a period of thirty-seven years. She had varicose vein injections for two and one-half years, and a vein ligation in 1931 gave transient improvement. Examination: On the inner aspect of the lower third of the right leg was a hand-sized erythematous and indurated lesion; the lower half was boggy with two punched-out ulcers each about 2 cm. in diameter. Ten treatments were given during a period of six weeks, at the conclusion of which the ulcers were healed and the tissues firm, although still pigmented. There was no evidence of return after six months.

CASE 3.—A. M., female, aged twenty-five years, had ulceration of eight years' duration following postpartum phlebitis. This had practically incapacitated the patient for eight years although occasionally the ulcer healed for a short period. She had been bedridden for seven months. Examination: Definite bilateral varicosities with pigmented, scaly, brawny, indurated area covering entire right ankle. Just below external malleolus was a punched-out, deep ulcer, about two and one-half centimeters in diameter. After twenty-one treatments with mecholyt iontophoresis during a period of one month, the ulcer was entirely healed. She was able to do her own housework at the end of the first week.

CASE 4.—M. A., female, aged seventy-five years, had varicose ulcers of twenty years' duration. Examination revealed palm-sized, erythematous, indurated, oozing area on lateral surface of the right ankle in the center of which was a weeping ulcer 4.5 cm. \times 5 cm. After thirteen treatments, given during a period of three weeks, the ulcer was completely healed. Treatments were continued for several more weeks to prevent the skin from breaking down. There has been no recurrence in four months.

CASE 5.—Patient U., female, aged sixty-two years, had varicose ulcers of twenty-five years' duration. No response to lotions and salves. Present ulcer, one year. Located on the lower third of the leg, the ulcer was 7 cm. \times 5 cm., very deep and surrounded by indurated, brawny tissue. Because of the severity of the condition, we gave this patient daily treatments but kept her ambulatory, nevertheless. The ulcer was healed after the fiftieth treatment. We have continued treatments to prevent breaking down of newly formed skin.

CASE 6.—R. S., female, aged forty-seven years, had a varicose ulcer of seven years' duration, located on lower third of leg. The ulcer was 1 cm. \times 2 cm. and surrounded by brawny tissue. The ulcer, although persistent, was not deep, and it was completely healed after five treatments, given on an average of twice a week.

CASE 7.—Patient C., female, aged fifty years, had varicose ulcers of twenty-three years' duration. The entire left leg, from the knee to the ankle, was brawny and indurated with numerous punched-out, scattered ulcers and one large ulcer 11 cm. × 6 cm. After the sixteenth treatment (three a week), all ulcers were healed. Treatments are being continued in an endeavor to get the skin in the best possible condition. Throughout the treatment this patient has continued to wash, iron, chop wood, and do all her usual household work.

CASE 8.—Patient J., female, aged fifty-one years, had a varicose ulcer of seven months' duration. Situated on the lower third of the leg was seen a very deep, punched-out ulcer, 2 cm. in diameter. This was healed in eight treatments.

CASE 9.—C. B., male, aged fifty-eight years, had bilateral varicose ulcers of thirteen months' duration. The ulcers had not healed following a variety of treatments, including x-ray therapy (eleven $\frac{1}{4}$ unit treatments) and vein injections with quinine urea. Examination showed bilateral ulcers on the lower third of the legs. The right measured 5.7 cm. × 4.6 cm., and the left 7.0 cm. × 4.9 cm. Both ulcers were completely healed after the thirteenth treatment.

TABLE III

THE TREATMENT OF VARICOSE ULCERS WITH ACETYL- β -METHYLCHOLINE IONTOPHORESIS

PATIENT	AGE IN YR.	DURATION OF ULCER (CONTROL PERIOD)	SIZE OF ULCER	NUMBER OF TREAT- MENTS	RESULT
1. S. N.	55	12 yr.	Induration 9 × 4 cm Ulcer 1.8 × 1.8 cm.	16	Healed
2. B. K.	62	37 yr. (Rarely healed)	2 ulcers, each 2 cm. diameter	10	Healed
3. A. M.	25	8 yr.	2.5 cm. diameter	21	Healed
4. M. A.	75	20 yr.	4.5 cm. × 5 cm.	13	Healed
5. U.	62	25 yr. total (Present ulcer 1 yr.)	7 cm. × 5 cm.	50	Healed
6. R. S.	47	7 yr.	3 cm. × 4 cm.	15	Healed
7. C.	50	23 yr.	Scattered ulcers, larg- est 11 cm. × 6 cm.	16	Healed
8. J.	51	7 mo.	2 cm. diameter	8	Healed
9. C. B.	58	13 mo.	Bilateral— Rt. 5.7 cm. × 4.6 cm. Lt. 7.0 cm. × 4.9 cm.	13	Healed

Above are reported nine cases with chronic varicose ulcers, all of which were completely and rapidly healed by the use of iontophoresis, using a 0.5 per cent mecholyl solution. No other treatment was used, and the patients were kept at their normal occupations. Thus far, we have had no failures. We realize that it is preferable to close the veins as part of the treatment, and, where feasible, we have recommended injection therapy at the conclusion of each experiment. If these results can be obtained in a large series, this form of treatment

has a definite place in the therapy of cases which do not heal after injections, of which there were several in our series, and in the cases of those patients to whom it is not desirable to give injections because of the presence of diabetes, phlebitis, or other contraindications. We have also used this method in the treatment of various other types of skin ulcers, such as those at the tips of amputation stumps, ulcers apparently due to cold sensitivity, and ulcers of unknown etiology. The results have been encouraging, but these represent only isolated instances in each condition and, hence, are not reported in detail. It is to be expected that, if the etiological factors are not removed, all ulcers of this type will tend to recur unless treatment is continued.*

DISCUSSION

The unexplored possibilities of the choline compounds, from the viewpoint of the pharmacology and therapeutics, should be the basis of much extensive research during the coming years. While the reactions which result from large doses of these compounds (and which are described as the muscarine, nicotine, and circulatory types) are essentially similar, there is, very evidently, on more careful study, a subtle difference in them. For instance, carbaminoyl-cholinechloride (doryl) appears to act somewhat more intensely on the gastrointestinal system but less intensely on the circulatory system than acetyl- β -methylcholine chloride (mecholy). On the other hand, the ethyl ether of β -methylcholine chloride, which is known to be more stable⁴⁷ but less active⁴⁸ than mecholy in body fluids, appears to be more effective in the production of sweating and salivation but less effective in its action on the circulation if used in equivalent pharmacological dosage subcutaneously. The ethyl ether is decidedly less effectual when given by iontophoresis.

Acetylcholine is also ineffectual when used with iontophoresis, and the reactions to subcutaneous injections in ordinary dosage (100 mg.) are almost negligible. We were able to produce, in certain individuals, typical choline reactions with dosages of 2,000 mg. orally administered.

A bromcholine ester (pacyl), dimethyl-dioxypurin-methan-carbon-acid-trimethyl-bromethyl-ammonium, which is very stable in body fluids, is being widely used abroad and is worthy of careful study. It has the advantage of being effective with small oral dosage (1 to 2 tablespoonfuls of pacyl, each of which represents 0.005 gm. of the compound) and is reported to follow closely the action of mecholy. We are unable to report on the effectiveness of this compound at this time but mention it as representative of many of the choline com-

*Since the preparation of this report a total of twenty-four cases of varicose ulcers have been treated with similar results. These will be reported in a later paper.

pounds which will of necessity be subjected to careful study in the near future. Some of these may prove to be much more satisfactory than any that are being used at present.

SUMMARY

1. The general reactions produced by large subcutaneous or oral doses of the more active choline compounds can be reproduced by iontophoresis, using the same drugs. In addition, there are certain local manifestations which appear at the site of application.

2. On the basis of our experiments there is no consistent, marked change in the basal metabolic rate resulting from the use of the choline compounds in the dosages indicated.

3. Although it is possible to produce a marked drop in blood pressure by the use of several of these compounds, this is a transient effect. We have not seen a single patient who has maintained a lowered blood pressure from the use of these drugs.

4. Iontophoresis with mecholyl has proved to be a palliative method for the treatment of arthritis.

5. In peripheral vascular disease, where organic occlusion has been the major factor, the choline compounds have not been of marked value.

6. In vascular disease in which spasm is the major factor, the use of the choline compounds, as outlined,⁹ has proved helpful.

7. A preliminary report on the successful treatment of long-standing chronic varicose ulcers is presented.

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ARTERIOLAR HYPERTENSION IN THE AMERICAN NEGRO*

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THE apparent increase in the incidence of essential or, better termed, arteriolar hypertension with its associated high mortality and attendant morbidity has furnished the impetus for extensive investigative work pertaining to its etiology and pathogenesis. The contributions from animal experimentation, although few in number, have been significant in that their results have made possible refutation of many of the older theories advanced. Nevertheless, the material accomplishments toward a solution of the problem have been attained principally through clinical research. A product of such study is the discovery of a greater prevalence of essential hypertension in the American negro than in the white race.¹ This racial difference in the incidence of primary hypertension, as will be subsequently developed, appears to be of great significance, particularly in view of the fact that the disease is practically unknown among the native African negroes. It is the purpose of this communication to offer an explanation for the occurrence and high incidence of the disease in the American negro and to point out the inadequacy and impracticability of some of the previously proposed theories as to the etiology of arteriolar hypertension.

CONSIDERATION OF THEORIES

Although the etymological qualification of the term "inheritance" has been grossly neglected, much of the voluminous literature on the subject is singularly dogmatic and concordant in support of the hypothesis that essential hypertension is inherited biologically. Based on inference and indirect evidence only, this opinion has prevailed from the time of Sir Clifford Allbutt,² who considered essential hypertension a "common hereditary peril," up until the present when Major³ promises the eradication of essential hypertension in one generation by statutory prohibition of the intermarriage of hypertensive families. An opportunity of putting this theory to test presents itself in the comparative study of the incidence of essential hypertension in the American negro of our section and his African cousins. The observations and studies of Shattuck⁴ in Liberia, Heiman and his associates⁵ in Johannesburg, Donnison^{6, 7} in East Africa, Taylor⁸ of the American Zulu Mission Dispensary, Odaley⁹ of the Gold Coast Colony, Dry¹⁰ of Northern Rhodesia, and Wakeford¹¹ of Southern Rhodesia concur em-

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phatically in the conclusion that essential hypertension is extremely rare and almost unknown among the native negro tribes of Africa. In comparison, as we have pointed out and wish to emphasize, their descendants, after a residence in this country of approximately two hundred years more or less, show an incidence of hypertensive cardiovascular disease two and one-half times greater than that of the native Americans. Objection to a comparison in this regard, on the score that heredity is no longer pure in the American negro, is to be anticipated. When applied to the American negroes as a whole such objection is perhaps justified, but, in the South, where black and white alike abhor the hybrid, interbreeding is at a minimum. The evidence of admixture with the white race in the negroes studied by us is negligible and insufficient to reconcile the disparity in the incidence of essential hypertension in the African and American negroes. Even so, to make the theory of inheritance applicable to the existing facts by attributing the incidence of essential hypertension in the American negro to interbreeding with the white race, it would be necessary to assume that all the subjects of our study were hybrids; and furthermore, inasmuch as the incidence of essential hypertension in the American negro is actually greater than that of the white race, it would be necessary to infringe on the mendelian law to explain the higher incidence of a character in the hybrid than in the parent carrying the character.

The difference in the incidence of essential hypertension in the American and African negroes might be attributed to change of climate for which the findings of Roddis and Cooper¹² may be offered in support. These authors observed the blood pressures of American Naval officers in the tropics to be on an average 11.5 mm. below the level considered normal in the temperate zone. These findings are not sufficiently conclusive to find application here, and they lack confirmation in the work of Foster¹³ in his study of the blood pressures of Americans and Europeans in China. In addition, there is no evidence which indicates that contrary circumstances would produce opposite results.

Amblard¹⁴ and others have implicated syphilis, and Barach¹⁵ has incriminated past infections as causative agents of essential hypertension. Syphilis and infectious diseases are notoriously prevalent in the American negro. However, when applied to the white race, the theories of syphilis and infections as causes of essential hypertension appear substantially refuted by the data compiled by Walker and O'Hare,¹⁶ Fishberg,¹⁷ Horine and Weiss,¹⁸ and Schulze, Ochsner, and Brown.¹⁹

Theories attempting to explain essential hypertension on the basis of malfunction of the kidneys with consequent retention of pressor-acting, protein metabolites come up for consideration here in view of a difference in the dietary of the African and American negroes. The native African negro subsists largely on a vegetarian dietary, whereas the

diet of the American negro is excessively rich in protein foodstuffs. Evidence relative to the effect of excessive protein ingestion on the blood pressures of experimental animals is disconcerting. Nuzum and his coworkers²⁰ reported a rise in the blood pressures of rabbits fed on a high protein diet, but such effects have been subsequently denied by Newburgh²¹ and Anderson²² in rabbits, and Drummond and his associates²³ and Osborne and his coworkers²⁴ in rats. Further, as Jackson and Moore²⁵ have surmised, were the evidence from such experiments decisive in incriminating protein food excess as a cause of hypertension, the clinical application of such facts would be another matter, for the conditions of these experiments are not applicable to man. That an excessive ingestion of protein may be a factor not innocuous is intimated by the classical therapeutic regimen employed in primary hypertension today in which protein foods are curtailed to minimal requirements. The rationale of such a plan of management has little to support it except custom, for clinical investigations are concordant in denying excessive protein intake a rôle in the etiology of essential hypertension. The conclusions of Mosenthal^{26, 27} are emphatic and are corroborated by the observations of Thomas²⁸ in studying the incidence of hypertension and nephritis in the Eskimos. Further confirmation is found in Lieb's report²⁹ on the physical status of Vilhjalmur Stefansson, the Arctic explorer, who subsisted for nine years on a meat diet exclusively.

The American negro is gluttonous, and many of the race are obese. Stengel³⁰ and Allbutt² considered overeating a cause of hypertension. More recently, Terry³¹ has reported on a study of a group of obese women, the majority of whom had hypertension; he also observed that frequently reduction in weight was associated with a concomitant lowering of the blood pressure. Slight reduction in weight, as in many of Terry's cases, effects a temporary reduction in blood pressure in a number of obese individuals with essential hypertension, but dietary restriction in normal and thin individuals without elevated blood pressures is capable of producing a similar effect. Not rarely we have observed in obese individuals with a fulminating type of hypertension a spontaneous reduction in weight accompanied by a rising blood pressure. The incidence of obesity and hypertension in the American negro woman is such that their fortuitous association could be anticipated to be frequent without a cause-effect relationship. The menopause, the innocuousness of which we are not willing to accept, also appears at the age when obesity and hypertension are more likely to be present. Our premise that the association of obesity and hypertension is not one of interdependence is substantiated by the findings of Alvarez and Stanley³² in a study of the blood pressures in 6,000 prisoners and 400 guards in whom they found obesity to have no relation to hypertension under the age of thirty-seven years. Schulze and his asso-

ciates,¹⁹ in a study of 927 cases of essential hypertension in individuals under the age of forty years, were impressed with the rarity of obesity in this group. Hartman and Ghrist³³ observed in analyzing the blood pressures of obese individuals otherwise normal that with an increase in weight there was an increase in the height of the normal systolic pressure without an associated rise of the diastolic pressure, a finding not comparable with the pressures encountered in essential hypertension in which the diastolic elevation is most characteristic. A careful consideration of the accumulated facts seems to justify the conclusion that, although obesity definitely aggravates a preexisting essential hypertension, there is no direct etiological relationship.

Riesman,³⁴ Hopkins,³⁵ and Alvarez and Zimmermann³⁶ contend that the menopause constitutes an unquestionable etiological factor of hypertension in women and offered in explanation the theory of disturbed endocrine balance initiated by an abnormal ovarian hormonal influence. The incidence of hypertensive cardiovascular disease is one and one-half times greater in the negro female than in the negro male.¹ A further significant fact is that the disease tends to appear decidedly earlier in life in the female than in the male. These facts, along with the great prevalence of castrates occasioned by radical pelvic surgery for fibroid tumors and venereal infections among negro women, warrant careful consideration of the menopause as a possible etiological factor of essential hypertension in negro women. Although Polak and his coworkers³⁷ and Lehfeldt³⁸ deny such cause-effect relationships, we have observed that negro women at the menopause, particularly surgical menopause, suffer much from emotional disturbances incident to this climacteric epoch; and, like Culbertson,³⁹ we find abnormal vacillations of the blood pressures in this group the rule, and established essential hypertension indeed common. As a direct cause of essential hypertension, the menopause leaves much to be explained: when considered, however, as an accessory factor, the effect of the menopause on emotional stability lends itself readily to logical correlation with the elucidation which follows.

Much has been written recently concerning the psychological characteristics of the hypertensive type of individual—the American business man who sacrifices all in his conscientiousness to attain success, worried, overambitious, and tense. To this psychical picture the American negro presents an exact antithesis; he is notorious for his lack of ambition, his indifference toward accomplishments, and his slovenly, care-free, easy-going disposition. Yet the negro is by no means stolid, nor does he have the platonic disposition of the Chinese. He is exceedingly emotional and syntonie, vibrating erratically with the environment. His responses to stimuli supplied by his surroundings are exaggerated and lacking in restraint. These overreactions are evident in all the emotions: in fear he is panicky; in happiness he becomes hilarious; in

love he is erotic; in reverence he is overly pious; and in anger he brandishes a weapon with intent to kill. On the other hand, the native African negro, according to Dry¹⁰ and Wakeford,¹¹ is indifferent, unemotional, apathetic, and disinterested. Unlike the Mexicans and Chinese in this country, the American negro has attempted to emulate his white brother's modern manner of living—that of “making life a problem rather than an art.” Although statutorily free, racial prejudice dictates, through custom, specific confines which are not insignificant additions to the intricacies of living like the modern American. These circumstances make syntony and emotional reactive resilience necessary to his life, and it is not improbable that the singular psyche of the American negro has been forced upon him by his environment. This is in accord with the view held by Moscheowitz⁴⁰ regarding the psyche of white patients with hypertension. The surroundings of the American negro require of him a responsiveness and perpetually bombard him with emotional stimuli in response to which he is unable to exercise restraint. The emotional instability incident to the menopause aggravates this inability to make a satisfactory adjustment to the environment.

The influence of the theories which embodied the organic explanation for the increase in peripheral resistance in primary hypertension has not as yet been erased. For this, the term hypertension itself is largely to blame in that it implies a static phenomenon. The lability of the blood pressure, first recognized by Gumprecht,⁴¹ emphasized by Mosenthal and Short,²⁶ and reiterated by Ayman,⁴² is the most singular characteristic of essential hypertension and is not sufficiently appreciated. These striking fluctuations of the blood pressure imply a morbid physiology, only the sequelae of which can be anatomical. In the opinion of Kylin⁴³ this lability of the blood pressure is explainable only on the basis of a vasomotor disturbance, which is in accord with the view of Norris and his associates,⁴⁴ who state that the vasomotor mechanism in patients with essential hypertension is sensitized and that hypertension in those instances is simply an exaggeration of a normal physiological blood pressure response. These contentions are substantiated by the findings of Mneller⁴⁵ that the diurnal and nocturnal fluctuations in blood pressure in normal individuals and in patients with essential hypertension differ only in degree, and that patients with essential hypertension show extreme reactions to stimuli which in normal persons would cause only mild reactions. That is to say, the blood pressure responses to emotional stimulation in the hypertensive and in the normal individual are qualitatively the same, the difference being only from a quantitative standpoint. That the ordinary and usual incidents of life provide stimuli sufficient to cause marked fluctuations in the blood pressures of patients with essential hypertension has been demonstrated by Brown,⁴⁶ O'Hare⁴⁷ and Mosenthal and Short.²⁶

Erroneously, essential hypertension has been considered a disease of middle life. Alvarez⁴⁸ directed attention to the frequent occurrence of abnormal elevations of the blood pressure in college students, and his contention that essential hypertension begins in youth is supported by the findings of Glomset.⁴⁹ Schulze and his associates¹⁹ concluded from a study of young persons with essential hypertension that clinically established hypertension under the age of forty is not rare. It remains to be shown that the so-called "emotional hypertension" and early essential hypertension are not one and the same; Ayman⁴² admits the extreme difficulty of differentiation. Diehl and Hesdorffer⁵⁰ have recently shown from a five- to ten-year follow-up study that individuals with intermittent or transient elevation of blood pressure during college years are more likely to have an elevated blood pressure after a period of from five to ten years than are individuals who show no emotional vacillations. That the vasomotor system is sensitized, perhaps in youth, by environmental influences much as reflexes in the central nervous system are capable of being conditioned by environment, is not unreasonable to consider. Reacting repeatedly to environmental stimuli by generalized arteriolar spasm, the arteriolar mesial musculature hypertrophies, thereby further enhancing the paroxysmal blood pressure elevations. Later, as a result of the trauma to the arterioles incident to the abnormal blood pressure excursions, arteriolosclerosis results. Herrick,⁵¹ Ayman,⁴² and Schulze and his coworkers¹⁹ have demonstrated that the lability of the blood pressure in patients with essential hypertension varies inversely with the degree of arteriolosclerosis. Thus, as a result of a hyperreactive vasomotor mechanism, the oft-repeated abnormal fluctuations in blood pressure provoked by environmental stimuli may be perpetuated, and persistent abnormal elevation of the blood pressure results. The blood pressure elevation is at first intermittent, later perhaps only remittent, and finally, with the advent of organic changes in the blood vessels incident to the trauma inflicted by the excessive blood pressure fluctuations, the blood pressure elevation is perpetuated. The limits of the present-day definition of essential hypertension includes only a late stage of what is, in all probability, a sequence of related events of common origin. The importance of the recognition of abnormal fluctuations in blood pressure as an early stage of essential hypertension becomes apparent, and the value of lability of the blood pressure as a prognostic aid, stressed by Ayman,⁵² becomes obvious. The rate of progress from the initial to the final stage and the amount of damage done to the cardiovascular system by the abnormal fluctuations in blood pressure appear to vary much with different individuals. As in practically all other types of cardiovascular disease, women tolerate the morbid physiology better than men. In the negro, hypertension, like cardiovascular disease of every other cause, takes a fulminating course, more severe in men than in women.⁵³ Whether the differences in this regard

between races and between sexes, respectively, are the result of a disparity in the material from which the cardiovascular system is made, or of a discrepency in the amount of exposure to stress and strain, promises long to be a moot question.

It is this concept of the pathogenesis of essential hypertension by which the origin of essential hypertension in the American negro and the discrepency in the incidence of this disease in the African and American negro, and in the American white race, is most satisfactorily explained at this time. The theory of the inheritance of a dominant character in essential hypertension finds no support here. The inheritance of a predisposition to hypertension can apply only so far as biological equipment to cope with situations is inherited and this would, by and large, be racial. It is the civilization which provides the situations to be met and hence, the exciting factor. Customs and racial prejudices provided by this civilization make the same environment more complex for some races than for others. The negro, biologically unequipped to cope with a complex environment, finds his nervous system subjected to much stress and strain during the process of attempted adaptation to occidental civilization. The vasomotor system, as an integral part of the nervous system, participates in this upheaval and becomes sensitized or conditioned to react with greater agility.

SUMMARY

Attention is directed to the significant fact that, although arteriolar hypertension is practically unknown among the native African negroes, the disease is unusually prevalent in their descendants living in this country, the incidence being actually greater than that in the American white race. The inadequacy of the theory of the biological inheritance of primary hypertension in this connection is stressed. The possible etiological rôles played by climate, diet, infections, and the menopause in the pathogenesis of hypertension in the American negro are discussed. On the basis of the neurogenic concept of the development of hypertension, a theory is elaborated to explain the origin of the disease in the American negro and to account for its high incidence. The importance of the environment as a causative factor is emphasized.

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CLINICAL RESULTS FROM ORAL ADMINISTRATION OF THEVETIN, A CARDIAC GLUCOSIDE*

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THE fruit of yellow oleander, termed the be-still nut in the Hawaiian Islands, yields a glucoside, thevetin, the digitalis-like action of which was first demonstrated by König and Husemann.¹ The exact potency of the crystalline product was recently established by Chen and Chen²—the frog minimal systolic dose being between 0.004 and 0.005 mg. per gram and the cat unit 0.85 mg. per kilogram, as compared with the frog minimal systolic dose of 0.0005 to 0.0006 mg. per gram and the cat unit of 0.12 mg. per kilogram for ouabain (G-strophanthin). According to the cat unit, thevetin is therefore approximately one-seventh as toxic as ouabain, weight for weight. Upon the conclusion of the pharmacological work, clinical investigations were undertaken by Arnold, Middleton, and Chen³ to determine its therapeutic possibilities. It was shown that by intravenous injection the digitalis-like property of thevetin could be readily substantiated. The pulse rate was diminished, compensation restored and maintained, and electrocardiographic changes similar to those caused by digitalis were regularly observed after its administration. No instance of local reaction or thrombosis attended its introduction by the intravenous route.

Our earlier studies³ included a few cursory observations upon the effects following the oral use of the tincture of defatted kernels and the solution of pure thevetin. By such a method of administration, circulatory improvement seemed obvious, but certain side actions upon the gastrointestinal tract, especially cramps and diarrhea, appeared at the same time, particularly with the tincture. A survey of the literature revealed that such symptoms as nausea, vomiting, and diarrhea were frequently encountered in poisoning cases from be-still nuts and in experimental animals intoxicated by thevetin. Balfour and MacLagen⁴ described the occurrence of nausea and a peculiar form of vomiting without distress or retching, but with diarrhea, in two boys who had taken the seeds of *Thevetia neriifolia*. They suggested that "the peculiar vomiting was perhaps an action of the stomach itself, unaided by the abdominal muscles and diaphragm." Descourtilz, cited by König and Husemann,¹ observed nausea as well as shivering and nervous manifestations in a negro who had eaten a kernel of the same plant. The fatal case of be-still nut poisoning

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TABLE
CLINICAL DATA UPON THE RESULTS OF

NO.	AGE	SEX	WT.	PRIOR DIGITALIS	THEVETIN DOSAGE	INTERVAL IN DAYS	STATUS % TOLER.	THERAPY MAINTEN.	INITIAL EFFECT			
									CIRCUL.		GAST.	INTES.
									SUMJ.	OBJ.		
1	73	F	200	0	M. xxv—q.i.d.	4	66	—	+	+	0	0
2	42	M	142	Irregular—1 year	M. viii—t.i.d.	16	—	+	0	+	0	0
3	65	M	118	Irregular in- fusion	M. viii—t.i.d.	6	—	+	+	+	0	0
4	50	M	142	Maintenance	M. xxv—q.i.d.	4	95	—	0	+	+	+
5	43	M	239	Irregular	M. x—t.i.d.	5	7	—	0	+	0	0
6	57	M	122	Irregular	M. viii—t.i.d.	26	—	+	0	+	0	0
7	74	M	?	Irregular	M. viii—t.i.d.	4	—	+	+	+	0	0
8	65	M	149	?	M. x—t.i.d.	6	13	—	0	0	0	0
9	54	M	108	0	M. xx—t.i.d.	3	45	—	0	+	0	0
After six days' rest												
10	68	M	180	Maintenance	M. viii—t.i.d.	8	—	+	0	0	0	0
11	55	M	?	Indefinite	M. xv—t.i.d.	3	?	—	0	+	0	0
Thereafter												
12	67	M	180	0	M. xxv—q.i.d.	3	55	—	0	0	0	+
After 4 days' rest												
13	64	M	181	0	M. xxv—q.i.d.	3	55	—	+	+	0	0
After 4 days' rest												
14	63	M	200	Irregular	M. xxv—q.i.d.	4	66	—	+	+	0	0
15	53	M	164	Inadequate	M. xv—q.i.d.	2	20	—	0	+	0	+
Thereafter												
16	36	M	131	Maintenance	M. viii—q.i.d. M. xv—t.i.d.	4 12	— 94	— —	0 0	0 +	0 +	0 0
17	67	M	122	0	M. xx—t.i.d.	4	55	—	0	0	0	+

*Symbolic value of thevetin therapy:

Circulatory advantage marked, +.

Circulatory advantage less marked and accompanied by minor gastrointestinal effects, ±.

Pronounced gastrointestinal effects and less marked circulatory response, †.

Predominant gastrointestinal effects and minor circulatory response, —.

Neither circulatory nor gastrointestinal effect, 0.

Unable to evaluate, ?.

I

THE ORAL ADMINISTRATION OF THEVETIN

FURTHER THEVETIN	SUBSEQUENT EFFECT				COMMENT	SYMBOLIC VALUE OF THERAPY*
	CIRCUL.		GAST.	INTES.		
	SUBJ.	OBJ.				
6 c.c.—1 day	+	+	+	0	Regular control of decompensation; minor nausea with anorexia.	+
0	-	-	-	-	Maintenance without adverse symptoms.	+
Maintenance	+	+	0	0	Unable to tolerate digitalis; no adverse effect—maintenance on thevetin.	+
Maintenance After 3 days' rest	+	+	0	+	Improved tolerance after rest; slight diarrhea after 11 days.	+
0	-	-	-	-	Maintenance without adverse symptoms.	+
0	-	-	-	-	Unable to tolerate digitalis; no adverse effect—maintenance on thevetin.	+
M. viii—t.i.d. 9 days	+	+	0	+	Diarrhea on 13th day.	±
0	-	-	-	-	No circulatory improvement nor adverse effect.	0
M. xx—t.i.d. 2 days	+	+	0	+	After slight diarrhea and then a rest, no adverse reaction on excessive doses of thevetin.	+
M. xx—t.i.d. 16 days	+	+	0	0		
0	-	-	-	-	No circulatory improvement nor adverse effect.	0
M. xv—t.i.d. 12 days	+	+	0	0	Regular control of decompensation. Advantage maintained; no adverse symptoms.	+
M. viii—t.i.d. 16 days	+	+	0	0		
M. xxv—q.i.d. 2 days	+	+	+	+	Early diarrhea continued with circulatory improvement; rest did not improve tolerance.	-
M. viii—t.i.d. 1 day	+	+	+	+		+
M. viii—t.i.d. 1 day	+	+	+	+	Improved circulation succeeded by slight anorexia and discomfort; after rest no adverse symptoms.	+
Maintenance	+	+	0	0		-
0	-	-	-	-	Inadequate response; no adverse effect.	?
M. xv—q.i.d. 7 days	+	+	+	+	Early diarrhea, but circulatory equilibrium reestablished before anorexia and nausea; maintenance without adverse effect thereafter.	+
Maintenance	+	+	0	0		-
Maintenance	0	0	0	0	Only adverse effect—slight nausea; not continued on maintenance dosage.	+
M. xx—t.i.d. after 2 days' rest—for 10 days	+	+	+	+	After early diarrhea, thevetin was pushed to therapeutic effect with slight anorexia and occasional loose stools.	- +

TABLE I—

No.	AGE	SEX	WT.	PRIOR DIGITALIS	THEVETIN DOSAGE	INTERVAL IN DAYS	STATUS % TOLER.	THERAPY + MAINTEN.	INITIAL EFFECT			
									CIRCUL.		GAST.	INTES.
									SURM.	OBJ.		
18	65	M	122	0	M. xx—t.i.d.	3	41	—	+	+	0	0
									After 3 days' rest			
19	54	M	126	0	M. xv—t.i.d.	4	31	—	—	+	0	0
									Thereafter			
20	57	M	186	Irregular	M. xv—t.i.d.	8	43	—	+	+	0	0
									After 12 days' rest			
21	66	M	145	Inadequate	M. viii—t.i.d.	5	—	+	+	+	0	0
22	50	M	130	0	M. xx—q.i.d.	7	136	—	0	0	0	0
23	45	M	147	?	M. viii—t.i.d.	7	—	+	+	+	0	0
									Thereafter			
24	45	M	147	Recent	M. viii—t.i.d.	4	—	+	+	+	0	0
25	64	M	161	Inadequate	M. xv—t.i.d.	3	18	—	+	+	0	+
									After 2 days' rest			
26	56	M	?	Recent	M. x—t.i.d.	5	?	—	+	+	0	0
									Thereafter			
27	64	M	178	Inadequate	M. xii—t.i.d.	5	14	—	+	+	0	0
									Thereafter			
28	64	M	170	0	M. xxv—q.i.d.	2	39	—	0	+	0	0
29	57	M	145	0	M. xx—t.i.d.	5	57	—	0	+	0	0
30	65	M	199	0	M. x—t.i.d.	5	8	—	0	+	0	0
31	52	M	183	Remote—none recent	M. xv—t.i.d.	8	8	—	+	+	0	0
									After 3 days' rest			
32	70	M	?	Inadequate—recent	M. xx—t.i.d.	2	?	—	0	+	+	0
									After 9 days' rest			

CONT'D

FURTHER THEVETIN	SUBSEQUENT EFFECT				COMMENT	SYMBOLIC VALUE OF THERAPY*
	CIRCUL.		GAST.	INTES.		
	SUBJ.	OBJ.				
M. viii—t.i.d. after 2 days rest—for 9 days	+	+	0	+?	Early vagal effect; delayed abdominal dis- comfort and occasional loose stools and cramps.	+
M. viii—t.i.d. 10 days	+	+	0	+		-
M. xv—t.i.d. 2 days	+	+	+	+	Improved circulation succeeded by anorex- ia, cramps, and diarrhea; maintenance thereafter with disappearance of ad- verse effects.	+
M. viii—t.i.d. 33 days	+	+	0	0		-
M. viii—t.i.d. 4 days	+	+	0	0	Conduction changes led to discontinuance; no adverse gastrointestinal effect. Later, nausea, vomiting and cramps on main- tenance dosage.	-
M. viii—t.i.d. 12 days	+	+	+	+		
M. xv—t.i.d. 7 days	+	+	0	0	Improved circulation without adverse ef- fects.	+
M. viii—t.i.d. 10 days	0	0	0	0	Neither circulatory nor adverse gastroin- testinal effect.	0
M. viii—t.i.d. after 5 days' rest—for 16 days	+	+	0	0	Improved circulation without adverse ef- fects.	+
M. xii—t.i.d. 36 days	+	+	?	0	Continued improvement with nausea on second day only.	
M. viii—t.i.d. 13 days	+	+	0	0	Steady circulatory improvement without adverse effect.	+
M. xv—t.i.d. 2 days	+	+	+	+	Early circulatory improvement succeeded by anorexia, nausea and slight diarrhea; after 2 days' rest, no adverse symp- toms.	±
Maintenance	+	+	0	0		
M. x—t.i.d. 5 days	+	+	0	0	Early circulatory improvement with later decline; no adverse symptoms.	+
M. viii—t.i.d. 2 days	-	0	0	0		?
M. xii—t.i.d. 6 days	+	+	0	0	Steady circulatory improvement without adverse effect.	+
M. xv—t.i.d. 20 days	+	+	0	0		
0	-	-	-	-	Slight early circulatory improvement; early death.	?
M. xx—t.i.d. 7 days	0	+	+?	0	Slowing of cardiac rate early; transient anorexia and distress on 10th day.	+
0	-	-	-	-	Slowing of cardiac rate; no adverse ef- fects.	+
M. xv—t.i.d. 2 days	+	+	0	+	Early circulatory improvement succeeded by diarrhea.	±
M. x—t.i.d. 2 days						
M. viii—t.i.d. 1 day	+	+	0	0		
M. viii—t.i.d. 15 days	+	+	0	0	Circulatory advantage maintained; diar- rhea stopped.	
M. x—t.i.d. 1 day	0	+	0	0	Discontinued by reason of marked vagal effect; nausea questionable. Very slow pulse led to discontinuance.	+

TABLE I—

NO.	AGE	SEX	WT.	PRIOR DIGITALIS	THEVETIN DOSAGE	INTERVAL IN DAYS	STATUS % TOLER.	THERAPY MAINTEN.	INITIAL EFFECT			
									CIRCUL.		GAST.	INTES.
									SUBJ.	OBJ.		
33	55	M	168	?	M. x—t.i.d.	4	8	—	0	+	0	0
34	57	M	150	0	M. xv—t.i.d. M. x—t.i.d.	1 5	18	—	+	+	0	0
35	73	M	153	0	M. xv—t.i.d.	5	34	—	—	+	0	+
After 3 days' rest												
36	53	M	175	Maintenance	M. viii—t.i.d. with tr. Bella. M. v—t.i.d.	6	?	+	+	+	0	0
37	54	M	?	Recent	M. x—t.i.d.	2	?	—	0	0	0	0
38	64	M	148	0	M. x—t.i.d.	3	7	—	+	+	0	0
39	24	M	145	Inadequate	M. xv—t.i.d.	6	41	—	+	+	0	0
After 3 days' rest												
40	57	M	259	Recent	M. xv—t.i.d.	3	11	—	—	—	+	+

in a child reported by Arnold⁵ showed nausea, vomiting, and diarrhea, but the child succumbed apparently to the cardiac effects of the toxic principle present in these nuts.

Blas⁶ gave thevetin to three dogs by mouth in amounts varying from 5 to 50 cg. The large dose, that is 50 cg., induced salivation in twenty minutes, nausea, vomiting, and diarrhea in one-half hour; whereas with the 5 cg. dose vomiting was delayed until one and one-half hours after its administration. A single necropsy in the series of four observations upon three dogs indicated congestion of the stomach and the liver. Blas stated that he detected thevetin in the vomitus and the liver of this animal. Similar gastrointestinal effects were noted by König and Husemann,¹ who, in addition, pointed out the digitalis-like action of thevetin, as mentioned above. By intra-

CONT'D

FURTHER THEVETIN	SUBSEQUENT EFFECT				COMMENT	SYMBOLIC VALUE OF THERAPY ³
	CIRCUL.		GAST.	INTES.		
	SCUL.	CUL.				
M. x—t.i.d. 2 days	0	0	0	0	Died 6th day. No maintained advantage nor adverse effect.	0
M. x—t.i.d. 6 days	+	+	0	0	Steady circulatory improvement without adverse effect.	+
M. x—t.i.d. 7 days	+	+	+	+	Early improvement in circulation with slight diarrhea; latter subsided on smaller dose to recur with some nausea.	±
M. x—t.i.d. with tr. Bella	+	+	0	0	Advantage maintained without adverse effect.	
M. v—t.i.d. 8 days						
0	+	+	+	+	Marked circulatory improvement without adverse effect. Slow pulse led to discontinuance.	+
0	+	+	+	+	No circulatory improvement nor adverse effect.	0
M. v—t.i.d. 6 days	+	+	0	0	Fibrillation disappeared; no adverse effect.	+
M. x—t.i.d. 3 days	+	+	+	+	Early distinct advantage lost, and discontinued because of nausea, vomiting and diarrhea.	±
M. viii—t.i.d. 12 days with tr. Bella	+	+	+	+		
M. v—t.i.d. 6 days						
M. x—t.i.d. 4 days						
M. xii—t.i.d. 7 days						
M. xv—t.i.d. with tr. Bella	+	+	+	+	Disproportionate diarrhea and nausea to later slight circulatory advantage.	-
M. v—t.i.d. 2 days						

venous injection in cats, Chopra and Mukerjee⁷ reported the stimulation of intestinal movements. They believed that this action was partly dependent upon the peripheral stimulation of the vagus, for the effect disappeared to a great extent upon the administration of atropine, and partly dependent upon the stimulation of smooth muscles. Stimulation of isolated rabbit's intestines was also observed by Chen and Chen.² In their work the minimal emetic dose was determined in both pigeons and cats. When compared with ouabain in cats, thevetin is one-fifth as emetic but one-seventh as toxic, gram for gram. The significance of these figures will be discussed in a later section.

The purpose of the present investigation is to ascertain, by oral administration of the solution of thevetin, the efficacy in cases of

cardiac decompensation and to record the frequency of untoward effects. The solution was so standardized that each cubic centimeter was equivalent to 1 cat unit. In most instances, it contained from 20 to 25 per cent alcohol.

RESULTS AND DISCUSSION

The results from the administration of the solution of thevetin to forty patients with varying degrees of circulatory failure are analyzed in Tables I and II. No election of subjects was attempted, and the dosage was calculated in cat units with due consideration for the body weight and the theoretical tolerance as in the case of digitalis formulated by Eggleston.⁸ In the more seriously handicapped, this end was sought in not less than four or five days as a rule. The clinical responses, of course, served as the ultimate guide to the thevetin therapy in all cases.

A gross evaluation of the effect of thevetin given by mouth may be gathered from a glance at the column designated "Symbolic Value of Therapy" in Table I. Nineteen patients showed marked circulatory advantage while eight others exhibited less marked circulatory improvement accompanied by minor gastrointestinal effects. In 3 patients (Cases 12, 17, and 39) there were pronounced gastrointestinal effects with less marked circulatory response, and in 2 others (Cases 20 and 40) there appeared predominant gastrointestinal effects with minor circulatory action. The results in 3 individuals (Cases 14, 26, and 28) were suggestive but questionable, and those in 5 additional patients (Cases 8, 10, 22, 33, and 37) showed neither circulatory nor adverse response. In a word, 27 of the 40 patients receiving thevetin by mouth had such circulatory improvements that the use of the drug was deemed definitely justifiable. In 5 patients the gastrointestinal reactions overbalanced the circulatory response so that the therapy of thevetin in them must be considered unsatisfactory. In 8 others neither beneficial nor adverse effects were observed with the doses employed.

The favorable results obtained by the oral administration of thevetin were comparable in all details to those produced by digitalis, or by thevetin intravenously injected.³ Thus, the slowing of pulse, relief of dyspnea, decrease in venous pressure, increase in vital capacity, diuresis, loss of edema, and typical electrocardiographic changes uniformly occurred. In two instances (Cases 3 and 6), thevetin was successfully substituted for digitalis to which both patients had become intolerant.

An examination of Table II will show that 24 of the 40 cases were practically free from untoward symptoms, while the remaining 16 developed varying degrees of gastrointestinal reactions—cramps and

TABLE II

SUMMARY OF CLINICAL DATA FROM 40 CASES IN TABLE I

CLINICAL OBSERVATIONS		NUMBER OF CASES	CASE NUMBERS
Circulatory Condition	Improvement	32	1, 2, 3, 4, 5, 6, 7, 9, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 27, 29, 30, 31, 32, 34, 35, 36, 38, 39, 40.
	Doubtful improvement	3	14, 26, 28
	No response	5	8, 10, 22, 33, 37
Untoward Symptoms	Symptoms absent or so mild as to be negligible	24	1, 2, 3, 5, 6, 8, 10, 11, 14, 16, 21, 22, 23(?), 24, 26, 27, 28, 30, 32(?), 33, 34, 36, 37, 38
	Gastric upset, only (anorexia, nausea, or vomiting)	1	29(?)
	Intestinal disturbance, only (cramps or diarrhea)	5	4, 7, 9, 18, 31
	Both gastric and intestinal manifestations	10	12, 13, 15, 17, 19, 20, 25, 35, 39, 40

diarrhea being more frequent than anorexia, nausea, and vomiting. The side actions of 11 (Cases 4, 7, 9, 13, 15, 18, 19, 25, 29, 31, and 35) of the 16 patients were so mild that the use of thevetin was continued or resumed after a rest. In 4 instances (Cases 12, 15, 17, and 40) the adverse effects preceded any evidence of circulatory improvement, but in others they appeared either simultaneously or some time after decompensation had been brought under control. As with other drugs, there is a great variation in individual susceptibility. For example, a few patients in the present series tolerated $1\frac{2}{3}$ cat units of thevetin, four times a day, without any discomfort, while others experienced cramps and diarrhea with $\frac{1}{2}$ cat unit, three times daily. As a whole, however, the larger the dose, the more frequent were the adverse symptoms. The diarrhea and other untoward effects caused by thevetin regularly disappeared within twenty-four to thirty-six hours after its withdrawal. Following a rest period, varying from two to twelve days, 9 individuals (Cases 4, 9, 13, 15, 16, 19, 25, 31, and 35) seemed to tolerate the drug better than at the beginning of the treatment, although in 7 others (Cases 7, 12, 17, 18, 20, 29, and 39) untoward symptoms returned upon the resumption of thevetin. It should be pointed out that a reduction of dosage was made in 8 of the 9 patients who exhibited an increase in tolerance. This leaves only one patient (Case 9), who after a lapse of time could take the initial dose without developing the diarrhea noted at the beginning.

In order to exclude the development of tolerance to thevetin, laboratory experiments were conducted with pigeons, cats, and isolated small intestines of rabbits. It was found that a minimal emetic dose injected by vein and repeated at various intervals (one to four days)

uniformly induced vomiting in both cats and pigeons. Strips of rabbits' small intestines, immersed in Tyrode's solution, contracted to the same height by repeated applications of thevetin, the concentration being 1:125,000. It is obvious that no true tolerance to the glucoside can be demonstrated.

To test the validity of Chopra and Mukerjee's⁷ claim that the action of thevetin was partly on the vagal endings of the intestines, three of our patients (Cases 35, 39, 40) were given tincture of belladonna along with thevetin, hoping that the intestinal upsets would be checked. As indicated in Table I, the side actions persisted in two cases in spite of the belladonna therapy. The disappearance of the symptoms in the third one (Case 35) remains a question as to whether it was due to the reduction of dosage or actually due to the desired effect of the belladonna. The results obtained with isolated rabbit's

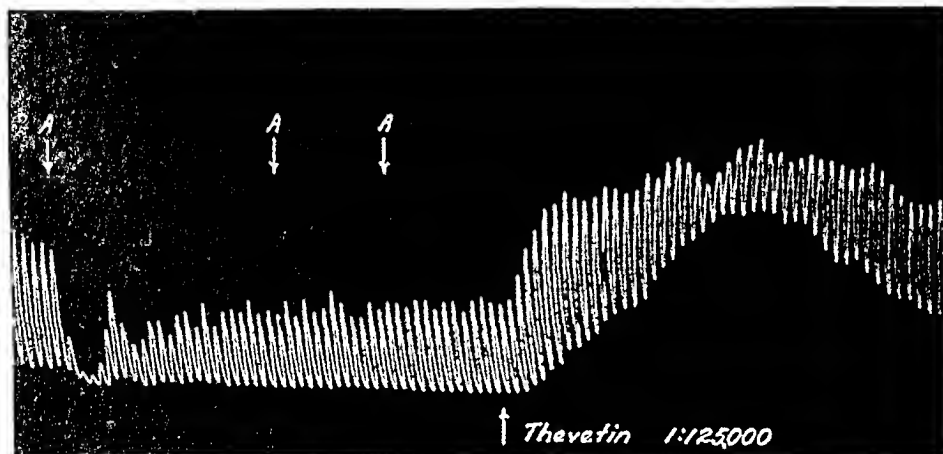


Fig. 1.—Action of thevetin on atropinized intestine.

A strip of the isolated small intestine of a rabbit was immersed in Tyrode's solution maintained at 38°C. At A, atropine sulphate was repeatedly applied until no further response was observed. Without washing, thevetin was added. A prompt response by stimulation resulted.

intestines appear to indicate clearly that atropine does not abolish the thevetin action, as shown in Fig. 1. It seems more logical to employ judiciously dilaudid or morphine to minimize the intestinal reactions, and to keep in mind that the toxic effects of the drug may be masked by such a procedure.⁹ This phase of the question is being subjected to further study.

It is possible to formulate an explanation for the relatively more frequent occurrence of gastrointestinal symptoms under thevetin therapy. The mechanism of vomiting caused by digitalis seems to involve a reflex action by way of nerve paths from the heart to the vomiting center in the medulla.^{9, 10, 11} The action of digitalis and its allies on the intestines "appears to be a direct one on the muscle itself."¹² Presumably, thevetin has the same *modus operandi*. With regard to the occurrence of untoward symptoms, even digitalis not

infrequently manifests its toxic effects before its therapeutic advantage is felt. There has been no satisfactory method of obviating the disturbing gastrointestinal action of the digitalis bodies without sacrificing their cardiac effect. It is admitted, however, that with thevetin the occurrence of cramps and diarrhea appears more conspicuous than anorexia, nausea, and vomiting as compared with digitalis. A scrupulous examination of the laboratory data will probably be helpful in elucidating the cause for such differences.

In Table III are listed the results of several crystalline digitalis-like substances, including thevetin, in cats. These figures are se-

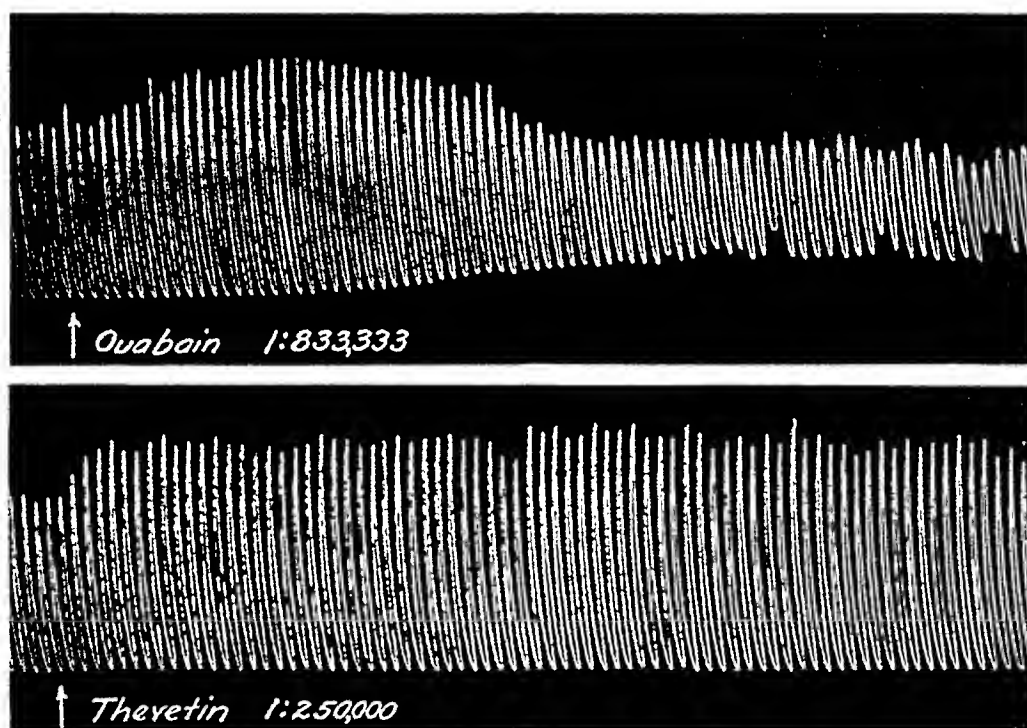


Fig. 2.—Comparison of minimal stimulating concentration of ouabain and thevetin on isolated intestines.

The preparation was similar to that in Fig. 1. The ratio of the concentration of thevetin to that of ouabain is $3\frac{1}{3}$:1.

lected from a previous publication.¹³ It will be noted that the minimal emetic dose of thevetin is equivalent to 35 per cent of the cat unit, as against 45 per cent for digitoxin and 50 per cent for ouabain. In other words, a physiological unit of thevetin is inherently more apt to cause vomiting than is either digitoxin or ouabain. With the isolated intestines of rabbits, twenty-three out of twenty-nine strips were stimulated by the minimal concentrations of thevetin and ouabain in the ratio of $3\frac{1}{3}$:1, as typified in Fig. 2, while the ratio of the cat units between the same is 7:1. This means that the amount of thevetin required to kill the cat is seven times that of ouabain, but the required amount of thevetin to stimulate the intestine is only three and one-third times that of ouabain. A deduction can thus be

made that a physiological unit of thevetin is approximately twice as effective as ouabain in stimulating intestines. These results certainly support our clinical observations upon the relative frequency of gastric and intestinal reactions, particularly the latter.

On the other hand, Table III also shows that it takes a smaller percentage of the cat unit for thevetin to produce early changes of the electrocardiogram in cats, such as P-R prolongation, bradycardia, and ectopic rhythm, than any other substance investigated. Arguing on the same basis as in the case of the gastrointestinal tract, a physiological unit of thevetin would be expected to be approximately twice as effective as ouabain or digitoxin in inducing early signs of digitalization. In the clinical studies, our original intention was to give by mouth the total amount of thevetin of theoretical tolerance within a reasonable period of time, much the same as in the case of digitalis; but it was soon found that circulatory improvement could be attained in the majority of cases with quantities of the drug below the theoretical tolerance, which is a confirmation of our laboratory results. It is not improbable that the incidence of cramps, diarrhea, anorexia, nausea, and vomiting may be further reduced by employing even smaller doses than those recorded in Table I. For example, in a frank case of cardiac decompensation with no previous use of digitalis or similar products, an initial dose of 1 cat unit, three times a day, may be tried. This amount should be increased if digitalization does not become apparent. Similarly, the maintenance dose may be diminished to $\frac{1}{3}$ cat unit, three times a day. These suggestions are being put to test, and a separate report will be made at a later date.

TABLE III

COMPARISON OF CAT UNITS: MINIMAL EMETIC DOSES AND ELECTROCARDIOGRAPHIC CHANGES OF SIX CRYSTALLINE CARDIAC PRINCIPLES IN CATS

DRUG	CAT UNIT IN MG. PER KG.	MINIMAL EMETIC DOSE		ELECTROCARDIOGRAPHIC CHANGES IN PER CENT OF CAT UNIT		
		MG. PER KG.	PER CENT OF CAT UNIT	P-R PROLON- GATION	MAXIMAL BRADY- CARDIA	ECTOPIC RHYTHM
Thevetin	0.85	0.300	35	17	30	31
Cino-bufagin	0.23	0.125	54	18	32	35
Areno-bufotoxin	0.41	0.150	37	37	53	50
Ouabain	0.12	0.060	50	37	58	54
Scillaren A	0.15	0.100	67	46	51	60
Digitoxin	0.33	0.150	45	48	56	61

The results with thevetin bear out certain features which may be particularly interesting to laboratory workers. In the investigation of a new digitalis-like principle or preparation, the mere determination of the cat unit or the frog minimal systolic dose is not sufficient

because it only sets the limit of toxicity. Electrocardiographic studies should give additional information as to its efficacy and promptness in inducing early signs of digitalization. Its emetic index and stimulating action on the intestines should be also qualitatively estimated. To be more specific, it is advisable to make accurate comparisons with ouabain and digitalis (or digitoxin) regarding the following points: (1) cat unit and frog minimal systolic dose, (2) percentage of cat unit to cause early electrocardiographic changes, (3) persistence of action in cats, (4) minimal emetic dose in pigeons and cats, and (5) minimal stimulating concentration to isolated intestines of rabbits. When these data are made available to the clinician, he will be in a better position to recommend proper therapeutic doses.

SUMMARY

1. A series of 40 cases of cardiac decompensation has been treated by the oral administration of thevetin. The results of twenty-seven cases were considered satisfactory because they were parallel to the action of digitalis in all details; those of five were dominated by untoward symptoms; and those of the remaining eight were classified as negative.

2. Thevetin may be advantageously used as a substitute for digitalis in patients who no longer show response or are intolerant to the latter drug.

3. Sixteen of the forty cases showed varying degrees of gastrointestinal effects—cramps and diarrhea being more conspicuous than anorexia, nausea, and vomiting. Of the sixteen, the reactions of eleven were so mild that thevetin therapy could be continued or resumed after a rest.

4. Laboratory data have been supplemented to explain the ease with which intestinal and gastric symptoms occur. Evidence has also been presented to show that by reduction of dosage the side actions may be further minimized without the sacrifice of circulatory response.

5. Attention has been called to the fact that, by more precise evaluation of a new digitalis-like drug, a more accurate estimate of the therapeutic dose may be made. The results of the present investigation indicate that thevetin should be employed in doses of fewer cat units than digitalis.

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FUNCTIONAL BUNDLE-BRANCH BLOCK*

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IN CLINICAL electrocardiography aberrant ventricular complexes of the type recognized as indicative of bundle-branch block have been generally accepted as a sign of diffuse myocardial disease. Recently, however, Wolff, Parkinson and White¹ have called attention to a group of cases, occurring mostly in otherwise healthy young persons subject to paroxysms of tachycardia or of auricular fibrillation, in which the electrocardiograms indicate a bundle-branch block and usually a short P-R interval. In some of the cases reported by these authors, spontaneously or following release of vagal tone by exercise or atropinization, the ventricular complexes have reverted to normal mechanism and the P-R interval has lengthened to be normal. They concluded that aberrant ventricular complexes generally recognized as indicating bundle-branch block may occur in healthy individuals with normal hearts and that the vagus nerve may be responsible for the occurrence of bundle-branch block curves. More recently Wolferth and Wood² have reported nine cases of similar nature, in only two of which was there demonstrable organic cardiovascular disease. A reversion of the electrocardiograms to normal could not be produced in any of their cases by exercise or by atropine. They believed that the abnormal mechanism consisted, not of a delay or block, but of an actual acceleration of the passage of the impulse from the auricle to a section of the ventricle. They suggested that the abnormal ventricular complex and the short P-R interval were caused by the passage of the sino-auricular impulse through an accessory auriculoventricular bundle similar to that described by Kent.³ This bundle was described by Kent as occurring in a certain percentage of mammals and as situated at the right lateral border of the heart. This work, however, does not seem to have been confirmed by other workers, and Lewis⁴ has opposed the idea that this abnormal path of conduction ever exists.

Previous to these observations, Wilson,⁵ Wedd,⁶ and Hamburger⁷ reported similar cases. Wilson in 1915 studied his case carefully and stated: "The normal rhythm when spontaneously present could be converted into an atrioventricular rhythm with right bundle-branch block by indirect or direct stimulation of the vagus nerves, and the abnormal rhythm when spontaneously present could be converted into the normal rhythm by the administration of atropine in doses sufficient to paralyze the vagi. This group of facts can lead to but one conclusion,

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and that is the vagi were partially responsible both for the change in the location of the pacemaker and the abnormality of the ventricular complex."

Our interest in this subject was aroused by the observation of two young, otherwise healthy Chinese who were prone to attacks of paroxysmal tachycardia and whose electrocardiograms during the inter-

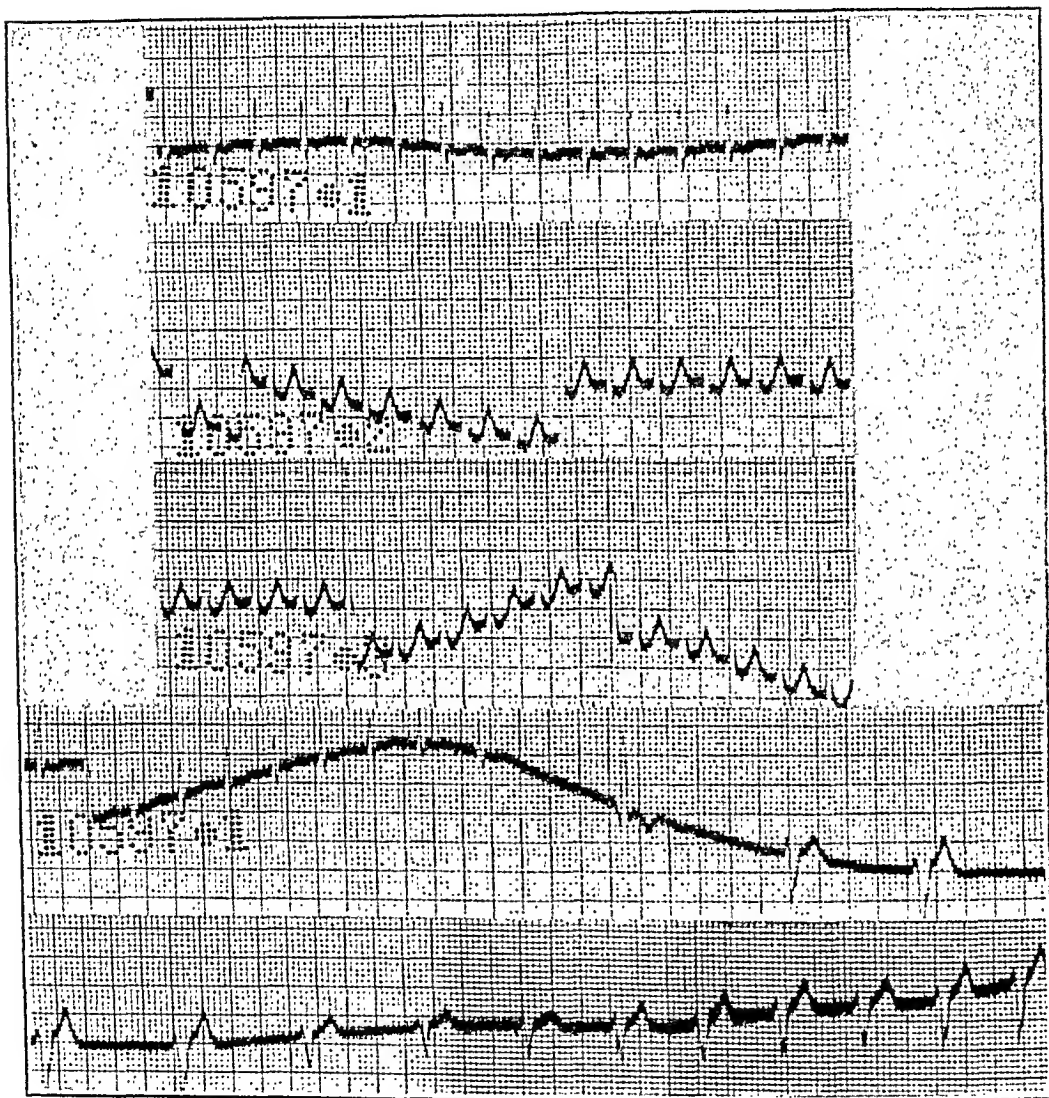


Fig. 1.—Case 1. Leads I, II, and III, above, taken during paroxysmal tachycardia. The third and fourth strips (Lead I) are continuous, showing the transition from tachycardia to bundle-branch block. In these and subsequent curves, each vertical line represents 0.04 second. Unless standardization shows otherwise, each horizontal ruling represents 0.1 millivolt.

val between attacks bore characteristics of bundle-branch block with short P-R intervals. There were three other individuals, not reported in this article, whose electrocardiograms had these characteristics but who did not give a history of paroxysmal tachycardia.

CASE REPORTS

CASE 1.—A healthy staff member of Peiping Union Medical College, aged twenty-nine years in 1932, had been under our observation from Sept. 16, 1929, until Sept. 13, 1934, when he left for a position elsewhere. He first complained of an attack of tachycardia on Feb. 9, 1932. The patient said that he had a similar attack nine years before and once again seven months before. Previous physical examinations and that made on the day after the attack revealed a slightly undernourished but healthy young man. The heart was not enlarged, and there was no significant murmur. Blood pressure was between 106 and 118 mm. Hg systolic and 60 to 70 mm. diastolic. Since then he had had frequent attacks of tachycardia.

A telerradiogram of the heart taken at a distance of two meters on Nov. 8, 1933, showed a heart which was normal in size and shape. Cardiothoracic ratio was 0.45.

Electrocardiograms were frequently obtained and the records during the attack of tachycardia—that showing the transition from tachycardia to bundle-branch

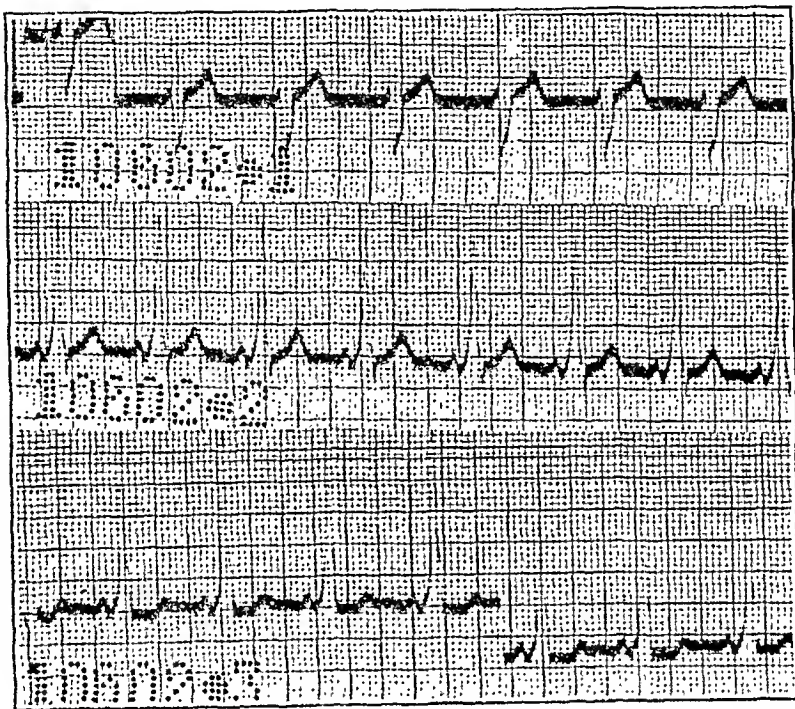


Fig. 2.—Case 1. Leads I, II, and III taken on the next day, showing right bundle-branch block. The curve taken just before the administration of atropine was similar to this.

block and that on the next day—are here reproduced (Figs. 1 and 2). The electrocardiogram in the interval would be generally considered as indicating a right bundle-branch block, with a deep and notched S-wave in Lead I, a widened QRS complex, and a short P-R interval.

On Nov. 9, 1933, two days after a short attack of paroxysmal tachycardia, the subject was given one milligram of atropine sulphate subcutaneously. Electrocardiograms were taken before the atropine, and ten, twenty, and thirty minutes (Figs. 3, 4, and 5) after atropine, and on the next day. There was a gradual, not abrupt, change in the form of the ventricular complex. The P-R interval remained short. The most conspicuous changes consisted, first, in the change of the direction of main initial ventricular deflection in Lead I, from an S-wave to an R-wave, and, second, in the marked shortening of the duration of the initial ventricular complex to normal in all leads. These changes were just as marked twenty minutes as thirty minutes after the administration of atropine. On the next morning a

Fig. 3.

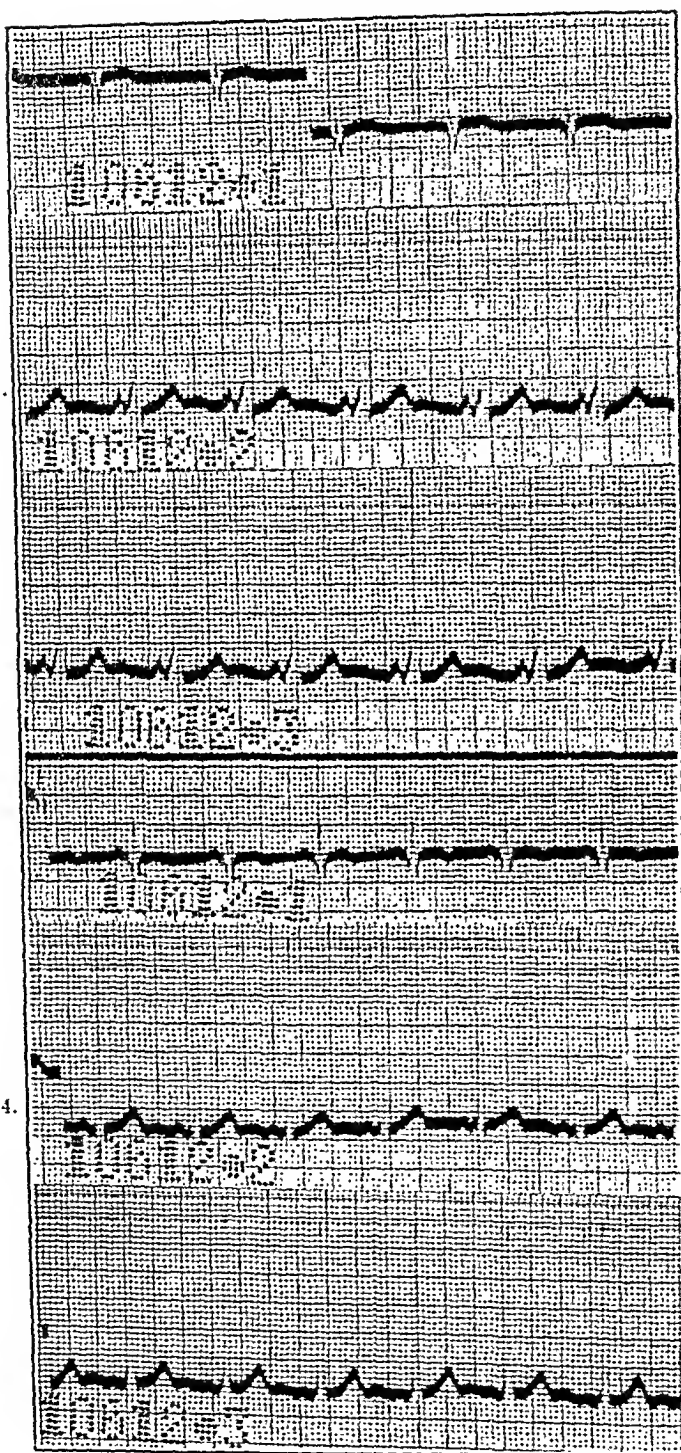


Fig. 4.

Fig. 3.—Case 1. Leads I, II, and III taken ten minutes after the subcutaneous administration of 1 mg. of atropine sulphate. Note the gradual change of the contour of the ventricular complex.

Fig. 4.—Case 1. Twenty minutes after atropine. Note the normal ventricular complex and normal electric axis.

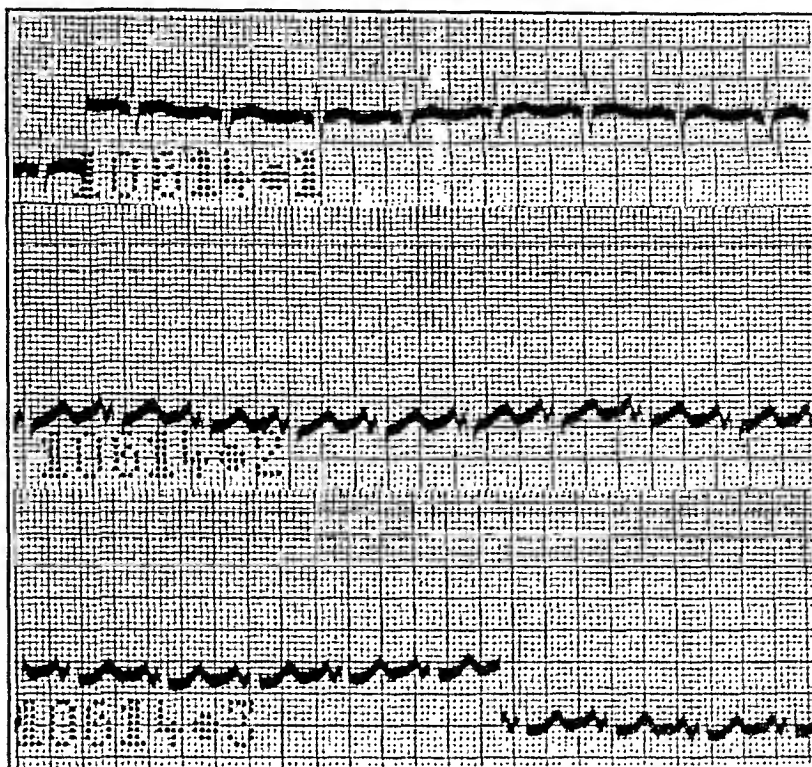


Fig. 5.—Case 1. Thirty minutes after atropine.

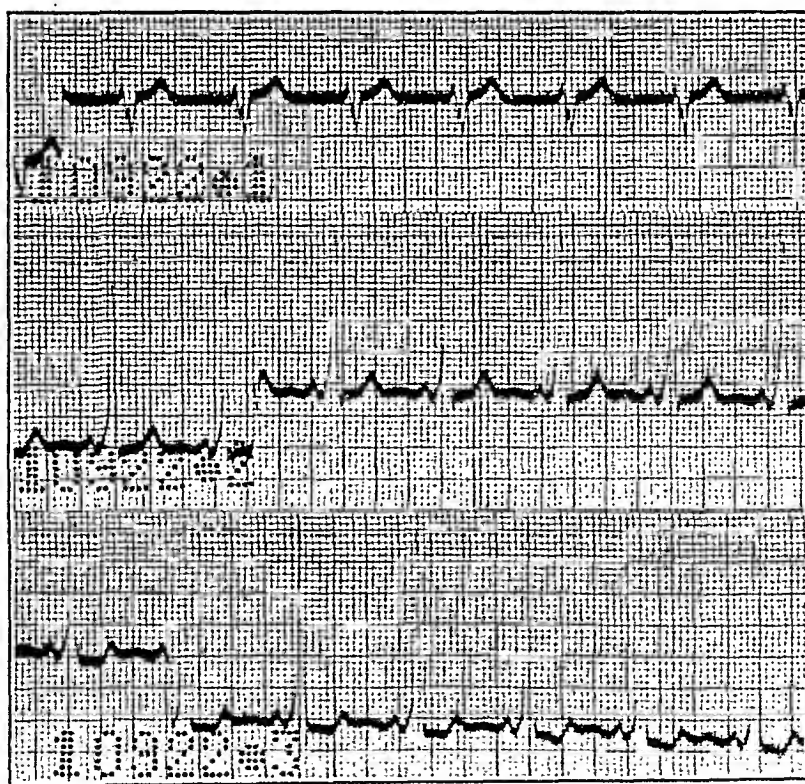


Fig. 6.—Case 1. Leads I, II, and III taken one year later.

reversion of the electrocardiogram to his usual form occurred. Subsequent records were also characteristic of right bundle-branch block curves (Fig. 6).

CASE 2.—A young Chinese male student twenty years old was admitted on March 6, 1934, for repeated attacks of palpitation of heart for eight years. First attack came on at the age of twelve years when the patient was playing, and passed off in a few hours. Sixteen months before admission he developed another

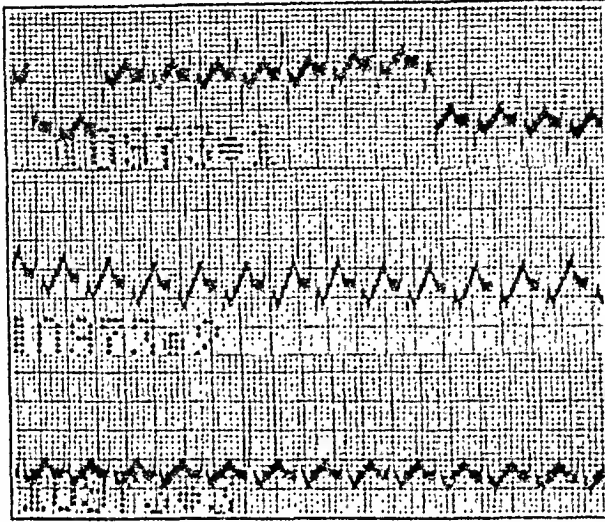


Fig. 7.—Case 2. Leads I, II, and III taken during paroxysmal tachycardia.

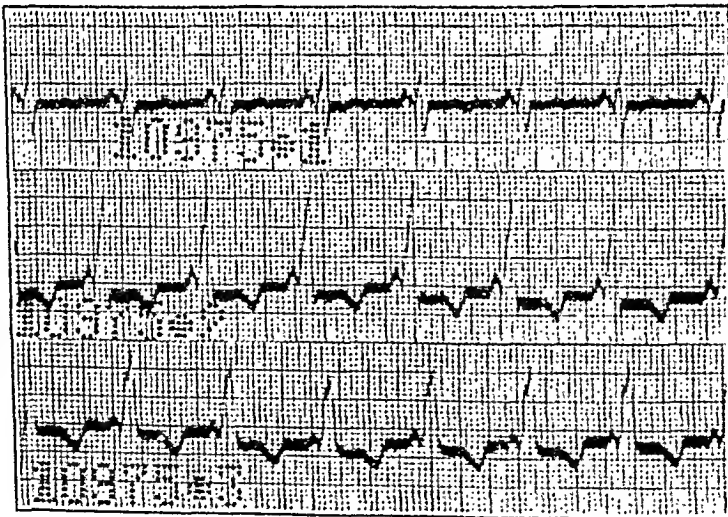


Fig. 8.—Case 2. Leads I, II, and III taken on the next day after cessation of tachycardia.

attack during play; the rapid heart rate was said to have persisted for five days. There were general weakness and some shortness of breath during that attack. The third attack recurred one month after the second. The fourth attack started on the day before admission, when he was climbing stairs. He had been entirely well between attacks. The past history was essentially negative. He was admitted for observation, when the usual methods used in reflex stimulation of the vagus nerve were tried without any effect on the abnormal mechanism.

Examination revealed a healthy young man, in bed, with profuse perspiration on his forehead. The respiratory rate was slightly increased—26 times per minute. There was no venous congestion. The heart was not enlarged. A teleradiogram of the heart showed it to be undersized by 14 per cent according to the method of Hodges and Eyster.⁸ The rhythm was regular and the rate rapid, 182 per minute. Radial pulse was small in volume. The attack ceased spontaneously at 3 A.M. on the morning after admission. Laboratory findings were essentially normal. An electrocardiogram was taken on the day of admission (Fig. 7). Several electrocardiograms taken after the cessation of the attack, the last one being taken two months after admission, were similar (Fig. 8). All of them showed short P-R intervals and prolonged QRS durations and low R-waves and short S-waves in Lead I.

On the third day after admission indirect vagal stimulation was attempted. It produced no marked effect on the electrocardiogram until double ocular pressure was employed. This procedure produced a definite change in the form of the R-waves

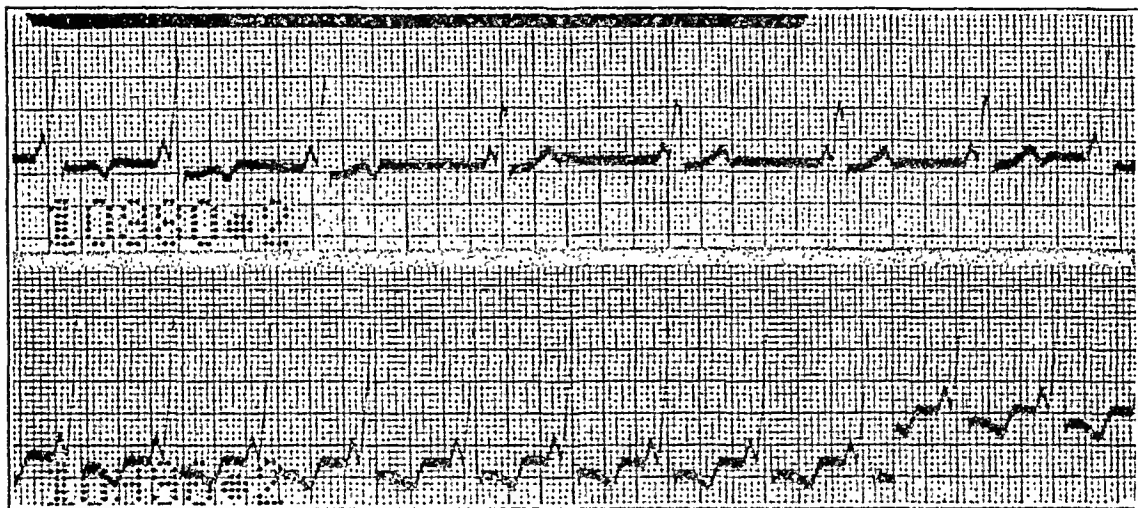


Fig. 9.—Case 2. Upper strip (Lead II) shows the effects of indirect vagal stimulation. The black line represents the time occupied by ocular pressure. The lower strip (Lead II) was taken twenty minutes after the subcutaneous injection of 2 mg. of atropine sulphate.

and T-waves and a slight alteration of the P-wave (Fig. 9). On release of pressure, the complexes reverted to his usual type.

Two milligrams of atropine sulphate were injected subcutaneously. This produced no change in the ventricular complex or in the P-R interval (Fig. 9).

DISCUSSION

These two cases present certain interesting features for discussion. Both of them bear witness to the definite influence of the vagus nerve on the ventricular complexes. In the first subject it appears that the vagus mechanism was at least partially responsible for the abnormalities of the curves since a small dose of atropine (1 mg.) could entirely change the abnormal form of the curves to one which was normal in every respect without even an axis deviation. It is difficult to suppose that a partial release of the vagal tone would deviate the passage of impulse from the hypothetical bundle of Kent, as suggested by Wolferth and Wood, to the usual auriculoventricular conduction path. The only

logical explanation would appear to be that the atropine released the vagal tone which was responsible for the delayed conduction through the right division of the His bundle.

The gradual change in the contour, duration, and axis of the initial ventricular complexes is also against the idea that the auriculoventricular conduction shifted from the accessory to the usual pathway.

Still stronger evidence against the conception of the existence of the right lateral bundle is the significant fact that the curves had the form of a definite right bundle-branch block in the first case and were suggestive of right branch block in the second case instead of a left branch block curve which would be expected if the auricular impulse arrived prematurely at the right ventricular musculature. Stimulation of the right ventricle as shown by direct observation on the exposed human heart⁹ always produces an aberrant ventricular complex in which the main initial ventricular deflection is upright in Lead I. Variation in the location of the bundle of Kent or the possible presence of other analogous auriculoventricular connections cannot explain the finding of right axis deviation of QRS in our cases since, even if there be such a path at the left lateral border of the heart, its distance from the sino-auricular node would make it improbable that it could transmit the auricular impulse to the ventricular musculature earlier than through the bundle of His.

In both of these cases, exercise or atropinization did not prolong the P-R interval as it did in some of the cases reported by Wolff, Parkinson, and White. Our findings are not out of harmony with the known action of atropine on the heart.

In the second case it should be remarked that a dose of atropine double that given in the first case produced no alteration in the ventricular complex. Indirect vagal stimulation, however, produced definite changes in both the initial and final ventricular deflections and also a slight change in the P-wave. This constitutes additional evidence that the ventricular complexes in the electrocardiogram of certain individuals can be altered by vagal stimulation.

In regard to the short P-R interval, which was 0.1 second in the first and 0.08 second in the second case, it appears that a rhythm originating in the upper part of auriculoventricular node is a satisfactory explanation. Experimental studies by Eyster and Meek¹⁰ and by Lewis and his associates¹¹ showed that stimulation of right vagus may cause the pacemaker to migrate from upper to lower portion of the sino-auricular node. Stronger stimulation may produce, in a certain percentage of animals, an auriculoventricular rhythm which, on further stimulation, may migrate from the upper to a lower portion of the auriculoventricular node. Eyster and Meek explained this downward shift of the pacemaker by assuming a gradual diminution in the vagus fibers supplied to the specialized tissue from sino-auricular node downward. Wilson¹² reported three cases in patients in whom an auriculoventricular rhythm

could, at certain times, be produced at will by deep respiration, which he regarded as analogous to vagal stimulation in animals. It is therefore probable that in these cases both the functional bundle-branch block and the short P-R interval are due to an increased vagal tone or an aberrant distribution of the vagus nerves.

The fact that these patients had paroxysmal tachycardia in itself indicates that during the attacks the pacemaker function was assumed by an ectopic focus. This strengthens the belief that in the interval between attacks the pacemaker might also be ectopic and be situated, as suggested, at the upper portion of the auriculoventricular node or its neighborhood. The occurrence of paroxysmal tachycardia has therefore some significance in relation to the shortened auriculoventricular conduction time, but its relation to the abnormal form of the ventricular complexes does not reveal itself.

SUMMARY

Two cases of functional bundle-branch block with short P-R interval occurring in healthy young subjects with normal cardiovascular systems are here reported. Both of the patients were subject to attacks of supraventricular paroxysmal tachycardia.

During attacks of paroxysmal tachycardia the QRS complexes in both cases were entirely normal in form, duration and electrical axis. Upon cessation of the attacks and during the interval between attacks, the electrocardiograms assumed the form of right bundle-branch block.

In one case, upon release of vagal tone by the administration of 1 mg. of atropine sulphate subcutaneously, the electrocardiogram gradually reverted to the normal mechanism with a normal electrical axis. In the other case, while atropinization produced no change in the form of the electrocardiogram, a distinct change in the form of the ventricular complex could be produced by indirect vagal stimulation. In both cases the electrocardiograms during the interval were characteristic of right, not left, bundle-branch block.

It may be concluded that:

a. Aberrant ventricular complexes of the type generally recognized as bundle-branch block may occur in healthy individuals without heart disease.

b. Vagal influence or aberrant distribution of the vagi may be responsible for intraventricular block in healthy subjects. Release of vagal tone may produce a reversion of the abnormal to normal mechanism.

c. Functional bundle-branch block, which is probably of vagal origin, occurs and is not a sign of heart disease.

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HEART FAILURE IN HYPERTENSION*

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THE most frequent cause of death of individuals with essential hypertension is heart failure. It has been estimated by various observers (Romberg,¹ Granger,² Murphy and his associates,³ Bell and Clawson,⁴ Scott,⁵ G. Fahr⁶) that between 50 and 80 per cent of patients who have sustained essential hypertension develop cardiac insufficiency from which they die. Fahr has calculated that hypertensive heart disease is the most common type of cardiac affection in people over the age of fifty years, and that nearly one-fourth of all deaths in the age group over fifty years are due to this form of heart disease. It is apparent that heart failure resulting from long-continued high blood pressure is a very common and important cause of morbidity and mortality.

There exists no well-defined conception concerning the cause of heart failure in hypertension. Myocardial failure from strain, cardiac muscle fatigue, and similar theories have proved inadequate explanations of circulatory failure in hypertensive subjects.

The present investigation was undertaken to determine whether a study of the post-mortem material from cases of hypertensive heart disease would throw light on the cause of the myocardial insufficiency.

MATERIAL

The clinical histories and post-mortem material of seventy cases of essential hypertension were studied. These seventy cases were divided into two groups. The first series (cardiac group) comprised forty patients with hypertension who presented the clinical picture of heart failure in their last illness. The usual signs of cardiac insufficiency—dyspnea, cyanosis, edema of dependent parts, swelling of the liver, cardiac arrhythmias, and fluid accumulations in the serous cavities, existed in varying combinations and degree. Several instances of sudden cardiac death were included in this group. The second group of cases served as a control. This series was composed of thirty patients with essential hypertension who died as a result of cerebral accidents, renal insufficiency, or coincidental disease, such as carcinoma, etc. None of the cases in this latter group manifested symptoms of heart failure.

The hearts of these seventy patients were studied by gross examination and dissection. Special attention was given to the state of the coronary vessels. In some of these hearts the coronary arterial system was injected with a barium-gelatin mixture after the method of Gross.⁷ X-ray films of such injected hearts afforded an excellent

*From the Laboratories and Medical Services of The Mount Sinai Hospital.

method for the study of the coronary vessels (Fig. 1). For microscopic study, blocks were cut from the ventricular myocardium, the interventricular septum, and, in some cases, from the papillary muscles. Sections were stained with hematoxylin eosin and elastic—van Gieson stains.

The hearts from a few of the cases included in this study were no longer available. We are indebted to Dr. Paul Klemperer for the use



Fig. 1.—Heart with coronary arteries injected after the method of Gross.

A, a break in the left anterior descending artery; B, the reduced and irregular lumen of the left circumflex coronary artery; C, the comparatively normal right coronary artery.

of the pathological descriptions in such instances. All the patients were from the medical services of Dr. B. S. Oppenheimer and Dr. G. Baehr.

The degree of coronary artery sclerosis is classified in two grades: (a) slight to moderate, and (b) marked. Slight to moderate involvement indicates some thickening of the arterial wall without significant

narrowing of the lumen of the artery. Marked sclerosis implies either localized or widespread pronounced lipocalcific intimal changes with considerably reduced or completely occluded lumen. In addition, careful note was made of the presence of old or recent thromboses in the coronary arteries.

The myocardium was examined grossly and microscopically. Microscopic infarctions, muscle thinnings, aneurysmal dilatations, diffuse fibrosis, and mural thrombi were noted. These changes were also identified in the microscopic study.

FINDINGS

In the cardiac group, 6 of the 40 cases (15 per cent) showed only slight or moderate sclerosis of the coronary arterial system. None of the vessels of these 6 hearts contained thromboses. These cases, which will be discussed later, represent an interesting group of patients with hypertension who die with clinical manifestations of cardiac failure and in whom autopsy fails to reveal sufficient organic cardiac change to account for the heart failure. The remaining 34 cases (85 per cent) had marked coronary sclerosis. In the severely sclerotic vessels of these 34 hearts, there were altogether 31 thromboses. The left anterior descending coronary artery was thrombosed in 13 hearts, the left circumflex in 6, and the right coronary artery in 12 hearts.

In sharp contrast there were only 3 cases (10 per cent) with marked sclerosis of the coronary arteries in the 30 cases of the noncardiac or control group, while the coronary system in the remaining 27 cases (90 per cent) had only slight or moderate sclerosis. None of the vessels in this group of hearts was occluded by either sclerosis or thrombosis. The findings in both groups are summarized in Tables I and II.

TABLE I
DISTRIBUTION OF SCLEROSIS IN CORONARY VESSELS

	LEFT ANTERIOR DESCENDING			LEFT CIRCUMFLEX			RIGHT CORONARY		
	SCLEROSIS		THROMBOSIS	SCLEROSIS		THROMBOSIS	SCLEROSIS		THROMBOSIS
	SLIGHT TO MODERATE	MARKED		SLIGHT TO MODERATE	MARKED		SLIGHT TO MODERATE	MARKED	
Cardiac (40 cases)	8	19	13	9	25	6	7	21	12
Noncardiac (30 cases)	27	3	0	27	3	0	25	5	0

Obvious myocardial scars, aneurysmal thinnings, and dilatations of the muscle and mural thrombi were present in 35 of the 40 hearts in the cardiac group. In the noncardiac group, only 5 of the 30 hearts showed grossly recognizable muscle changes. The other specimens showed hypertrophy of the chamber walls and papillary muscles.

TABLE II
DEGREE OF SCLEROSIS IN CORONARY ARTERIAL SYSTEM

	NUMBER OF CASES	GRADE OF SCLEROSIS	
		SLIGHT TO MODERATE	MARKED
Cardiac	40	6 (15%)	34 (85%)
Noncardiac	30	27 (90%)	3 (10%)

Microscopically, the musculature of the hearts in the cardiac group reflected the severity of the arterial changes. Areas of myocardial necrosis with leucocytic infiltration and large areas of fibrous replacement characterized many of the sections. The muscle fibers were hypertrophied, and there was an increase in the amount of interfascicular fibrosis. It must be noted that, in the six instances in which marked coronary artery changes did not exist, there were nevertheless some myocardial alterations represented by fibrosis and scarring. In the control group of noncardiac cases very marked or severe alterations in the structure of the myocardium were absent. Hypertrophied muscle elements, increase in interfascicular and intrafascicular fibrosis and occasional small patches of fibrotically replaced muscle fibers constituted the essential changes. Large scars, abundant fibrosis, or areas of recent myomalacia did not appear. Neither the type nor the extent of the pathological changes could be considered significant.

Hypertrophy of the left ventricle and, in many cases, of the right ventricle also, existed in the hearts of both groups of cases. This hypertrophy was seen directly in the thickening of the ventricular musculature, the interventricular septum, and papillary muscles. It was further confirmed by an increase in the weight of the hearts.*

In summary it can be said that in the great majority of the hearts of patients who died of hypertensive cardiac insufficiency, there was consistent involvement of the coronary arterial system. The changes in these vessels were marked arteriosclerosis, either generalized or localized, with narrowing of the arterial lumina. Thrombotic or atherosclerotic closure of a main vessel was frequent. Corresponding severe myocardial changes also occurred. In the noncardiac group the coronary system was only slightly affected. Very moderate arteriosclerosis without significant narrowing was the usual change. Coronary artery occlusion from either arteriosclerosis or thrombosis was conspicuous by its absence. Generally the myocardium reflected these minor coronary arterial changes in the relative absence of any pronounced alterations.

DISCUSSION

George Fahr⁸ was the first to point out that heart failure unassociated with chronic valvular disease in the great majority of cases (75 per cent) was accompanied by hypertension. Christian⁹ observed

*Detailed tables will appear in the reprints of the article.

a systolic pressure of 170 or over in 45 per cent of 400 cases of so-called chronic myocarditis. The validity of the association between elevated blood pressure and heart failure has been definitely established (O'Hare, Calhoun, and Altnow¹⁰). Strangely enough, no completely satisfactory explanation for the failure of the heart in hypertension has been evolved.

The commonly proposed reason for heart failure in hypertension is final inability of the muscle to work against the increased burden of the heightened blood pressure. There is an impressive array of clinical observation which makes it difficult to accept this simple and seemingly plausible theory that the myocardium of the healthy heart functioning against an increased pressure becomes diseased and fails (Hill).¹¹ Hypertrophy, which is muscle response to increased work, cannot be considered a pathological state. The efficiency of a heart with hypertrophied nondiseased muscle is not impaired. Lewis¹² points out that in draught and racing horses, and in racing dogs, that is, in animals whose hearts are subjected to long-continued and repeated strains, chronic cardiac maladies are practically unknown. Furthermore, in man, marathon runners and racers do not present a group whose mortality is higher than that of the general population. In a study with the x-ray and the electrocardiograms of 46 ricksha pullers, it was observed that 45 per cent showed definite cardiac enlargement.¹³ This cardiac hypertrophy probably was a physiological response to rapid exertion carried on daily for a period of years. There was no indication that the cardiac enlargement constituted or predisposed to heart disease. Coarctation of the arch of the aorta, a congenital malformation which causes a pronounced rise in blood pressure in that portion of the aorta proximal to the narrowing, imposes a strain on the heart which it bears without embarrassment for many years. Patients with this condition die from a variety of causes in the fourth and fifth decades of life. The long duration without cardiac symptoms in coarctation of the aorta, as in cases of essential hypertension, weakens the case for the direct association between increased work and the eventual myocardial failure. It is impossible to rule out the influence of the new factors which might be introduced in the course of years. The effects of infections and toxic agents, or more particularly arteriosclerosis, which invariably is prominent in the later years of life, are of the greatest importance.

Others have reported anatomical changes in the coronary systems and myocardiums of patients who died of hypertension. Most of these workers do not comment specifically upon the occurrence of coronary vessel disease in that group of hypertensive subjects who die of heart failure. Bell and Clawson⁴ found that only ten per cent of hypertensive hearts (not only cardiac deaths) were free of coronary arteriosclerosis, that fifty-five per cent were moderately, and thirty-five

per cent severely, affected. From a study of 420 cases of hypertension they conclude that coronary sclerosis is more intense and more frequent in hypertensive than in nonhypertensive cases. Furthermore, they state that two-thirds of all instances of coronary sclerosis are associated with hypertension. S. A. Levine,¹⁴ who analyzed 146 cases of coronary thrombosis, concluded that a previously existing hypertension was probably the most common single etiological factor in the development of coronary thrombosis. Murphy, Grill, Pessin, and Moxon³ studied 375 patients with hypertension, of whom 188 died of heart failure. They considered this group separately and found that 44, or 25.7 per cent, had gross coronary involvement. They remark, however, that "obviously coronary arteriosclerosis was more common than these figures suggest, but only the cases are included in which the coronary disease was advanced enough to produce definite heart disease and failure." They do not report the incidence of coronary artery lesions in those who died of cerebral vascular accidents, renal insufficiency, or intercurrent disease. Clawson¹⁵ studied the hearts of 115 patients who had hypertension and who died of cardiac failure. Only 12 of these 115 cases, i.e., about 10 per cent, had no coronary sclerosis. In 42.5 per cent of the cases the coronary sclerosis was severe. A. M. Fishberg,¹⁶ who studied the question for many years, writes: "Since I have been following closely the state of the coronary arteries in such patients (hypertensive cardiacs) it has seemed to me that coronary arteriosclerosis is the most common cause of cardiac failure in hypertensive patients." Scott¹⁷ records that more or less coronary arteriosclerosis is almost always found in hypertensive heart failure. Pardee¹⁸ has observed that, if individuals with hypertension develop cardiac symptoms, the clinical picture is similar to that of a patient with coronary artery disease. He is of the opinion that, as long as coronary arteriosclerosis is absent in hypertensive patients, cardiac symptoms will not appear.

From the foregoing it appears that close observers of both hypertensive and cardiac patients agree that the important factor in hypertensive heart failure is coronary arterial involvement. From our analysis herewith presented substantiation of these conceptions is obtained.

Besides the coronary artery sclerosis with narrowing and coronary artery occlusions from arteriosclerosis and thrombosis, pronounced myocardial lesions were found. In the presence of coronary occlusions large infarcts and infarct scars constituted the lesions. In addition, it was noted that there existed diffuse interfascicular and intrafascicular fibrosis to a greater extent than was present in the control group.

It is relevant at this point to discuss the origin of myocardial fibrosis in hypertension. In a paper published in 1924 Clawson¹⁹ says

that it exists only when coronary sclerosis is present and that there is not sufficient evidence to maintain the view that strain causes myocardial fibrosis. In a later publication¹⁵ he states that the myocardium is not severely involved in those cases with coronary sclerosis, although he makes clear that the presence of myofibrosis without coronary artery changes is not uncommon. He concludes that myocardial fibrosis is of slight significance as a cause of heart failure. Victor Levine²⁰ comes to the same conclusions concerning the frequent lack of correlation between coronary artery sclerosis and myocardial fibrosis. Because of this discrepancy, which he found frequently illustrated in the twenty-seven hypertensive hearts he studied, Levine invokes the theory of a functional disturbance in the fine vascular channels (Ricker).²¹ Lisa²² studied the myocardium of ten cases of decompensated hypertensive hearts. He described areas of granular degeneration with and sometimes without a cellular reaction. Later these cells—usually mixed collections—receded, leaving miliary scars. Other myocardial changes called to his mind the picture of an acute myocarditis. Stains for bacteria and the spirochetes of syphilis were negative. Unfortunately, Lisa did not mention whether or not coronary sclerosis was present. Lisa and Ring²³ studied 100 cases showing myocardial infarction or fibrosis at autopsy. They found 83 per cent of these hearts with moderate to marked coronary arteriosclerosis and 24 per cent with thrombosis of a coronary vessel. Hypertension had existed in 60 per cent of the cases. Madelaine Brown²⁴ analyzed 110 cases of myocardial fibrosis (chronic fibrous myocarditis) and found disease (thrombosis and sclerosis) of the coronary arteries in 70 of the cases. She advances the suggestion that coronary arterial disease is the most important etiological agent in the causation of myocardial scarring.

In cases in which the myocardial changes result from coronary artery disease, the involvement may be in either the large or small radicles of the coronary system. According to A. M. Fishberg,²⁵ small vessel involvement occurs in only 3 per cent of cases. This author emphasizes that arteriosclerosis involving the larger vessels is much more frequent in essential hypertension than arteriosclerosis of the smaller arteries. We can confirm the findings of Fishberg respecting the minimal involvement of the smaller vascular elements in hypertensive hearts.

It seems logical to conclude that the widespread myocardial changes which existed in such greater degree in the cardiac group than in the control hearts resulted from the more pronounced artery changes which were found in this group. This correlation readily makes clear the reason for the heart failure in the cases of hypertension which have these changes, for it is acknowledged that coronary artery disease is a factor in heart failure only through its influence on the myocardium.

Although it appears clear from the present study that coronary artery involvement is very frequently found in the hearts of hypertension patients who die with the clinical picture of heart failure and that undoubtedly the heart failure is the result of the coronary artery disease, it is not definitely stated that the hypertensive state stands in any etiological relationship with coronary arteriosclerosis. Nor can one say with absolute certainty whether or not episodes of cardiac breakdown experienced by such patients before the fatal illness were also the result of coronary arteriosclerosis and myocardial insufficiency.²⁶ However, when one considers the extent of the arterial involvement and the gradual progression of the arteriosclerotic process, it is more than probable that the earlier attacks of heart failure were accounted for by pathological changes similar to those found at autopsy.

Although in the vast majority of cases in the cardiac group sufficient organic changes in the coronary arterial system and myocardium were found to explain the final cardiac failure, there remain the six cases referred to above, in which there were no pronounced macroscopic or microscopic anatomical changes in the heart. Yet these six patients, too, displayed the symptoms of myocardial insufficiency, and death occurred from what appeared to be heart failure.

Chronic pulmonary conditions (bronchitis, emphysema) were present in three of these cases and accounted for the only cardiac symptom, i.e., dyspnea, displayed by the patients throughout life. In each of these cases a severe and rapidly spreading bronchopneumonia ushered in the terminal episode which was characterized by signs and symptoms of cardiac failure, due undoubtedly to the combined effects of the chronic and acute pulmonary conditions. The hypertension played a secondary rôle and actually contributed very little to the production of heart failure. The microscopic examination of the myocardium revealed no significant changes.

The remaining three cases represent a small yet important group* of patients with hypertension who demonstrated the symptoms of heart failure for some time before death. Autopsy did not reveal coronary artery disease of marked degree. Examination of these hearts did not reveal extensive myocardial changes. Although comparatively infrequent, myocardial failure in the absence of acute myocardial damage or coronary artery disease (sclerosis with narrowing, or thrombosis) occurs. It is seen often enough to have stimulated a great deal of speculation and some research. In the earliest treatises on heart failure myocardial insufficiency was considered to be the sole cause for circulatory failure. Romberg,²⁷ who studied the cardiovascular system in infections, emphasized the myocardial changes. This view was likewise projected by Krehl²⁸ in a series of publications. Soon it became apparent that frequently there

*Cases of this type will form the basis of a separate publication.

was insufficient anatomical change in the heart muscle to account for heart failure (Asehoff and Tawara²⁹). Romberg²⁷ had suggested that the toxic agents in infectious disease not only affected the myocardium but also had an influence on the peripheral vascular network. This first announcement of the important rôle of the peripheral system in circulatory failure received substantiation in subsequent studies on shock and rapid blood loss (Wenkebaeh,³⁰ Kisch³¹). More recent treatises give great prominence to this view (Benjamin,³² Schottmüller,³³ Blalock³⁴).

Eppinger attempted to explain cardiovascular failure in heart disease on the basis of a disturbed peripheral cellular metabolism (Eppinger, Kisch, and Schwarz³⁵). Today many believe that the alterations in glycogen and lactic acid metabolism so thoroughly investigated and described by Eppinger and his coworkers *follow* the slowing of the blood stream which accompanies heart failure and that they do not initiate the circulatory insufficiency (Barcroft,³⁶ Jervell³⁷). Once established, these metabolic changes probably complete a vicious cycle and contribute to the circulatory inefficiency. In fact more recently Eppinger himself considered the incomplete resynthesis of lactic acid to glycogen in the peripheral musculature of decompensated cardiacs due to a functional disturbance of the capillary bed. This results from anoxemia which is caused by a slowed blood stream arising from poor heart action (Eppinger, Laszlo, Schürmeyer³⁸). The studies of Eppinger have served to give the periphery a renewed and prominent, although not primary, place in the explanation of circulatory failure.

There is again today a definite trend to ascribe heart failure to a primary insufficiency of the myocardium. For instance, Rothchild, Kugel, and Gross³⁹ have recently shown that in the great majority of cases of chronic rheumatic cardiovalvular disease, myocardial failure is determined by the presence of the active lesions of rheumatic fever in the heart muscle. The mechanical effects of the valvular lesions are well borne into the sixth, seventh, and eighth decades if the muscle is not acutely involved and if other factors such as coronary arteriosclerosis and thrombosis with myocardial degenerations are absent.

Nevertheless, because there are cases such as the three now being discussed which do not present muscle lesions and in which the myocardial changes cannot be ascribed to the effects of infection, or to coronary artery sclerosis and thrombosis, the chemical factors in cardiac muscle physiology have been studied. Kutshera-Aichberger⁴⁰ found a reduction in the phosphatide (lecithin) and calcium content of the heart muscle of patients who died of circulatory failure. Laszlo,⁴¹ T. R. Harrison and his coworkers^{42, 43} have also reported lowered phosphate and potassium values in such hearts. The results obtained in animal experiments have confirmed the findings in man. According to these

theories, disturbed chemical balances and irreversible reactions in overworked muscle produce an accumulation of residual metabolites, anoxemia, poor nutrition of the myocardium, and eventual failure. Examination of such hearts at autopsy reveals hypertrophy and dilatation of various chambers dependent upon local circulatory obstructions, but microscopic examination of the heart muscle in some of these cases may not show marked or widespread changes—surely not enough to account for the failure of the heart as an organ. Heart failure here seems to be on a purely functional basis. Much work remains to be done before these chemical explanations of myocardial dysfunction are acceptable.

In attempting to account for failure of hypertensive hearts without pronounced organic changes in the coronary arteries or muscle, great importance has been ascribed to the fact that there really exists a relative insufficiency of the blood supply in these hearts. This is brought about even in the presence of normal coronary arteries by the increased requirements of an hypertrophied heart with greatly increased muscle mass functioning against the added burden of hypertension. The muscle suffers from this slight but long-continued deprivation and eventually fails. Some support for this conception can be derived from a report by Calhoun and his coworkers,⁴² who studied the relationship between the thickness of the ventricular muscle fiber, the heart rate, and length of diastole in patients with enlarged hearts. These workers concluded that the slow rate is advantageous to subjects with enlarged hearts "because the recovery period of the heart is prolonged, i.e., it takes oxygen longer to diffuse through a thick fiber than through a thin fiber." They reasoned from this that hypertrophied hearts beating at normal rates may fail from relative anoxemia present under these conditions. It cannot be stated that either unusually low or rapid heart rates occurred in our patients. It is, however, the fact that all had hypertrophy of the left ventricle, and most of the right ventricle, too. The increased muscle mass placed a continued increased demand for oxygen upon the circulation to the heart. Coronary arteriosclerosis with narrowing of the lumen or coronary thrombosis, when it exists, further increases this "circulatory debt."

Severe myocardial changes without sufficient arterial involvement to explain them are relatively uncommon in cases of hypertensive myocardial insufficiency. Likewise, cases of sudden death from heart failure without either a coronary thrombosis or marked myocardial change is unusual. In the series here presented three such instances were encountered. The comparative rarity of such cases emphasizes the fact that most commonly heart failure in hypertension is associated with coronary artery sclerosis and thrombosis and with the effects that such alterations produce in the myocardium.

SUMMARY

In order to investigate the cause of heart failure in hypertension the hearts of forty hypertensive patients who died with symptoms of myocardial insufficiency were studied. As a control group thirty hearts from patients with hypertension who died of cerebral accidents, renal insufficiency, or incidental disease were likewise studied.

Thirty-four (85 per cent) of the cases in the cardiac group had significant coronary arterial involvement (sclerosis or thrombosis), whereas only three (10 per cent) of the cases in the control group had significant coronary artery disease.

The myocardial changes in both groups reflected roughly the extent and degree of coronary artery involvement.

In six (15 per cent) of the forty cardiac cases there was not sufficient organic change in the coronary arteries or myocardium to account for the heart failure. Three of these six patients had marked pulmonary complications. Theories seeking to explain the cause of the heart failure in the remaining three cases are reviewed.

CONCLUSION

Cardiac failure in hypertension is occasioned in the great majority of cases by coronary artery sclerosis and thrombosis which cause degenerative myocardial changes and eventual myocardial insufficiency or sudden death.

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Department of Clinical Reports

TRAUMATIC RUPTURE OF THE RIGHT AURICLE WITH PATIENT SURVIVING NINE WEEKS

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THE history of this case is published for two reasons: first, its extraordinary medical interest, survival for nine weeks after rupture of the right auricle; and second, its unusual medicolegal aspects.

The case came before the Industrial Accident Commission of the State of California on the claim on behalf of the widow that the death was proximately caused by "an accident received in the course of and arising out of employment."

On the basis of the hospital record and the testimony of medical and lay witnesses, two esteemed internists submitted the opinion that the man's illness and death were "nonindustrial," i.e., not due to the alleged trauma but to a diseased condition of the heart. The Commission denied the claim.

Later, Dr. Edwin Merrithew, of Martinez, Calif., who had attended the man, with the attorney for the widow submitted the case to me for my opinion. It seemed that there were a number of features in the clinical history that had not been brought before the examiners or had not been considered by them: first, the normally low blood pressure in the auricle; second, the abnormally low systolic pressure exhibited by the patient; third, the extraordinary strength of the man, his big barrel chest, and his phlegmatic temperament. Moreover, there is quite extensive literature on traumatic rupture of the heart, with some six cases reported in which the patient survived for eight days after rupture of an auricle.

On this review of the clinical history and study of the literature, the Commission reopened the case, and after taking much medical testimony, finally submitted the matter to a panel of three physicians—Dr. Eugene S. Kilgore, Dr. Herbert Allen, and Dr. William Ophüls, all of San Francisco. These gentlemen rendered an unanimous opinion that the injury was the cause of death and that it was "industrial." The Commission then reversed its former decision finding in favor of the widow.

Perhaps the strongest circumstances favoring the opinion were the autopsy findings of a huge hemopericardium, the blood for the most part clotted, an aperture in the wall of the right auricle covered with

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clot, and especially the indisputable x-ray evidence of an immense pericardial shadow which preceded pericardial puncture (Fig. 1) and which persisted.

The following account is largely an abstract of sworn testimony presented at the various hearings, to which some items are added from personal interviews and correspondence.

J. A., aged forty years, a Portuguese dairyman, was a powerful man, 5 feet 5 inches in height, weighing about 200 pounds. His duties were milking and the breaking in of young cattle to be milked by hand and by the milking machine, a hazardous occupation. He was frequently hurt, but being stocky and stout was not much disturbed by being bruised and knocked about. His employer testified that A. worked for him a number of years, in fact up to the time of the accident, often "wrestling with cows. He was awful strong man."

On or about June 24, 1930, while milking a cow, he was kicked in the left lower chest by another cow, was knocked over, and was unconscious for a short time; he



Fig. 1.

Fig. 2.

Fig. 1.—Roentgenogram made July 7, 1930.

Fig. 2.—Roentgenogram made July 16, 1930.

was helped to his feet and walked outside the milking shed, but presently (after ten to twenty minutes) returned to his milking. He tried to work for several days after the accident but was very sick, complaining of pain and shortness of breath.

On July 1 he fainted and was carried into the house. This induced him to consult a physician, which he did on July 2, nine days after the accident. Dr. Merrithew said he complained that "he was sick, thought he had 'flu' and couldn't get rid of it." According to the physician, he seemed not to connect his illness with any injury. The doctor described him as a large man who did not look sick. Examination showed "heart sounds muffled, the area of cardiac dullness greatly increased; systolic blood pressure low (90)." Tentative diagnosis: Myocarditis with dilatation. The patient was advised to go to the hospital, but he objected. A heart tonic, rest and restricted diet were ordered.

On July 7 A. returned to the doctor, unimproved; he was sent to the hospital where his pulse was recorded as 90-96; temperature, 98.6° F.; respiration, 26. X-ray examination showed an enormous pericardial shadow, very dense (Fig. 1). Diagnosis: "Pericardial effusion, probably bloody."

July 10, aspiration of pericardium was performed with large trocar at inner end of left sixth interspace; Dr. Merrithew stating that he removed "a good quart of dark but apparently decomposed blood, which, however, coagulated quickly." Patient did not faint, nor did he show any considerable symptoms of shock from withdrawal of so much blood, nor did the cannula wobble (Merrithew). The blood flow stopped spontaneously. From these facts it seems fair to infer that the blood was not drawn directly from the circulation.

Five hours later x-ray examination showed no perceptible change in the size of the pericardial shadow.

July 11, a second aspiration was performed, about one pint of blood of similar character being evacuated. There was no reaction, but seven hours later the pulse

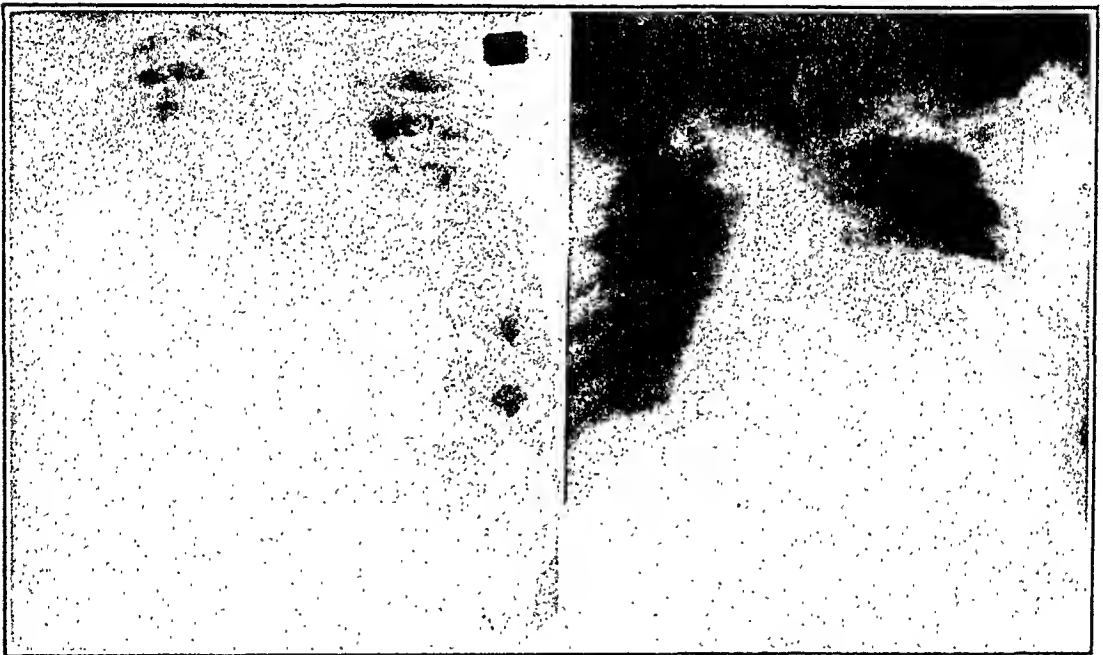


Fig. 3.

Fig. 4.

Fig. 3.—Roentgenogram made August 10, 1930.

Fig. 4.—Roentgenogram made December 21, 1929.

became irregular and difficult to count, and patient began to cough. Pulse rate was 102, soon coming down to 90; temperature, 101° F. After ¼ grain of morphine, patient slept practically all night, beginning to cough again in early morning, and then the pulse became irregular.

On July 12 patient became restless and nervous; pulse, 120; temperature, 100-100.6° F.; respiration 30-24; pulse at times irregular; cough troublesome.

On July 16, the x-ray examination showed pericardial shadow considerably larger (Fig. 2) apparently complicated with right pleural effusion, probably inflammatory. With rest in bed, his condition improved; the temperature dropped; the pulse gradually went down to 100 then to 90; respiration, 24-20.

On August 4, x-ray examination showed pericardial and pleural shadows still larger.

On August 5, the third aspiration withdrawing about a pint was performed. Pulse and respiration became quite rapid, the former 100-130; the latter 44-56, with slightly subnormal temperature.

On August 9, there was loss of appetite and considerable precordial pain.

On August 10, x-ray examination revealed: Pericardial shadow still larger with pleural effusion more marked (Fig. 3).

On August 13, patient was well enough to sit up in a chair; pulse, 104-118; respiration, 28-26.

On August 15, he left the hospital against advice, walking. Wassermann reaction was negative.

On August 25, he reentered the hospital; pulse, 130; respiration, 32. Condition progressively worse. Dr. Merrithew judged that operative opening of pericardium was necessary.

On August 26, under ether anesthesia, patient suddenly expired as the skin incision was being made. The chest was not opened.

An autopsy was performed by Dr. Buckmann, local health officer, shortly after death, Dr. Merrithew being present. Permission for the autopsy had been reluctantly given by the widow only on condition that no tissue be removed from the body.

The pericardium was enormously distended with fluid blood and clot, a large part of the clot laminated and adherent to the pericardium and the heart. Dr. Merrithew estimated the amount of clot at the almost unbelievable amount of 5 pounds or more, but the clot was not weighed. After the heart was removed from the body, a thin layer of old clot still adhered to the wall of the right auricle, removal of which exposed a rupture, $\frac{1}{2}$ to $\frac{3}{4}$ inch long, showing healing at the edges. The heart was not dilated, was about the size of the man's fist and of firm consistency. The valves were normal. There was considerable fat about the ventricles but no evidence of myocarditis. Both coronary arteries were slit open in the examination and found normally patent. There was much fluid in the right chest; the right lung was almost completely collapsed; the other organs were normal.

While the finding at autopsy of an immense laminated blood clot within the pericardium offers an adequate explanation of the failure of aspiration of a quart of blood to lessen the size of the heart shadow, it is probable that after release of pericardial pressure, bleeding from the rent in the auricle which may have ceased was either started up again or was accelerated. For some hours after the second and third aspirations there was restlessness and thirst. After the third tapping, one medical witness testified that the first reaction was relief of dyspnea then "shock, from which however he speedily recovered."

In brief, the argument for the plaintiff was that the deceased was an unusually powerful, hard-working and un-ailing man, stockily built, a stoical individual who had worked at hard labor continuously until the moment of the blow; that thereafter he worked but little, and then with great difficulty; that there was great pericardial effusion at least from the date of the first x-ray plate, July 2, until his death seven weeks later; that aspiration of a quart of blood did not lessen the size of the pericardial shadow; that at autopsy this fact was explained by the amount of solid laminated clot; that a rupture was found in the right auricle, its edges showing evidences of healing; that it was partially sealed over by adherent clot; that six patients in the literature were known to have lived eight days after rupture of an auricle; that rarity did not exclude the possibility of a patient living longer under par-

ticularly favorable circumstances such as obtained in this unusually strong man; that the flow from the auricle was probably slow, even intermittent, because of the normally low pressure in the auricle, the resistance afforded by the clot, and the abnormally low systolic blood pressure (it was only 90 when first recorded, nine days after the accident); that there are in the literature many cases in which rupture of the heart has occurred as a result of blows at a distance, some of them in which the heart was normal.

The argument for the defendant was that the case as claimed was unique; that no one had been known to live more than eight days after rupture of the auricle; that rupture of the heart even if induced by an injury was nearly always due to degeneration of the heart wall, fatty or arteriosclerotic; that the autopsy was not performed by a trained pathologist; that no tissue was removed that could be subjected to expert histological examination; that the heart was probably diseased; that macroscopic examination, even in expert hands, was not sufficient to exclude disease of the wall of the auricle; that men had been known to work with a considerable degree of myocarditis.

Whether one agrees with the claim that the rupture of the auricle occurred on or about June 24, 1930, nine weeks before death, the evidence is uncontrovertible that the man lived seven weeks after the first x-ray plate was taken and the pericardium aspirated. Even on the basis of the only remaining possible hypothesis that the auricle was slit by the trocar on July 10 and the blood withdrawn directly from the auricle, an hypothesis sufficiently negated above, the survival was still nearly seven weeks.

Being personally greatly interested because it was on my review of the story at the instance of the attending physician that the Commission reopened the case, and not being satisfied as to the condition of the patient's heart before the kick of the cow and learning accidentally that the patient had been in the hospital for a few days some six months previously, I made several trips to the dairy, talked to the man's widow and his employer, and reviewed the record in St. Joseph's Hospital, Stockton, Calif. The employer stated that A. had been in his employ many years; that he had never known him to be ill until December, 1929, nor to have had any serious accident; that during an epidemic of influenza in December he was taken ill with abdominal pain and distention but persisted in working for several days until it was evident that he was seriously sick, when he decided to go to the hospital; that he returned after ten or twelve days and did his regular work for the following six months until kicked by the cow; that in the meantime he seemed perfectly well and worked hard nine or ten hours a day; and that between milking times he was not idle. In reply to questions he stated that patient was not known to have lain down to rest in the daytime, but kept busy, on occasions even hauling water to cattle in the dry pasture, filling the

trough with a bucket from barrels; that his color was always bright, never blue; that he was not short of breath; that his legs did not swell; but that after the kick he was "never good for much."

At St. Joseph's Hospital, Stockton, he was under the care of Dr. L. R. Johnson (since deceased) who left no personal record. The hospital record stated that he entered hospital Dec. 17, 1929. Chief complaint: "Very much gas formation, both in stomach and intestines; some relief after belching; great distention; much pain; no headache; no backache; appetite good but food would not stay down; vomiting; he had been ill for two weeks with stomach trouble; no childhood diseases; severe attack of pneumonia at eighteen years; good recovery; no operations; health very good until present illness." Bedside record showed that the highest temperature was 101° F. on December 19; highest pulse 90; urine, sp. gr., 1.020; negative for albumin and sugar; leucocytes 11,000, 75 per cent polymorphonuclears. Blood pressure not recorded. He was examined by Dr. Jesse Barnes, internist, in consultation, who noted "definite conjunctival icterus, large area of dullness at right base posteriorly nearly to angle of scapula." The hospital report continued: "X-ray film showed marked enlargement of heart to right and left; suspect pericarditis with effusion. Final diagnosis: Influenza. Condition on discharge: Cured."

DENOUEMENT

The above mentioned x-ray plate, taken Dec. 21, 1929 (Fig. 4), is very faint, but it shows a large pericardial shadow difficult to interpret. It is not greatly different from that in Fig. 1, but, since it is evident that the x-ray tube was quite close to the patient, there is some considerable magnification of the heart shadow. It seems almost impossible that the patient could have worked, as testified by his employer, for six months after this plate was taken unless the condition was merely that of big heart, but the shadow may have been due to pericardial effusion, which was Dr. Barnes' diagnosis. At autopsy the heart was apparently of normal size. When these facts were brought to the attention of Dr. Merrithew, he expressed doubt as to the date of the kick by the cow. He said it might have been in December, 1929. The witnesses of the kick of the cow were ignorant Portuguese dairy hands. Was it possible that the employer, being interested in securing the indemnity for the widow, falsified the date of the kick? The records of the Insurance Company showed that the policy was taken out two years before December, 1929, the date of the first illness.

Was the auricle ruptured previous to the December illness, the patient living until the following August—eight months?

Department of Reviews and Abstracts

Selected Abstracts

Harris, I., Jones, E. Wyn, and Aldred, C. N.: Blood pH and Lactic Acid in Different Types of Heart Disease. *Quart. J. Med.* 16: 407, 1935.

Under resting conditions lactic acid in the blood is increased in cases of heart failure. The amount of lactic acid stands in a definite relation to the degree of heart failure.

Apart from extreme cases the pH of the blood is normal in different types of heart disease.

The amount of lactic acid formed after a standard exercise stands in a definite relation to the cardiac reserve power. The greater the degree of heart failure the greater the amount of lactic acid formed by standard exercise.

AUTHOR.

Cohn, A. E., and Steele, J. Murray: The Influence of Frequency of Contraction of the Isolated Mammalian Heart Upon the Consumption of Oxygen, *Am. J. Physiol.* 113: 654, 1935.

Experiments are described which confirm the observation that the rate at which dogs' hearts beat in heart-lung preparations influences the consumption of oxygen directly. The results reported were observed in two sorts of experiments:

1. In those in which the hearts were driven by induction shocks.
2. In others in which they were not further influenced than by the nature of the preparation itself.

In both methods the change in the rate of consumption of oxygen progressed roughly one-half as fast as change in the rate of contraction. Electrical stimulation itself had no effect on the rate of metabolism.

AUTHOR.

Cohn, A. E., and Steele, J. Murray: The Metabolism of the Isolated Heart of Dogs Related to Age. *J. Clin. Investigation* 14: 915, 1935.

Decrease in the consumption of oxygen with age was observed in heart-lung preparations made in pure bred female wire-haired fox terriers of known age living under similar environmental conditions and having been given similar food. Those variable factors in the life of the preparation which could be arranged were controlled; the effects of those which were uncontrollable were calculated. The degree of relationship between age and consumption of oxygen per unit of weight of heart was considerably less when account was taken of certain functions found to be related to both (age and oxygen consumption) but was still significant.

The evidence suggests that, although rate of contraction, size, and, in intact animals, the amount of work done play a part in the decrease of metabolism with age, there is, in addition, a change in structure of the heart or in its composition with age which leads to reduction in the amount of oxygen consumed by each unit of its weight.

A technical observation is believed to be of sufficient importance to deserve mention in the conclusion. When the lungs are exposed to ether even for brief periods, they are likely to become edematous—but apparently not otherwise.

AUTHOR.

Friedman, Ben, Clark, Gurney, Resnik, Harry, Jr., and Harrison, T. R.: Effect of Digitalis on the Cardiac Output of Persons With Congestive Heart Failure, *Arch. Int. Med.* 56: 710, 1935.

The effect of digitalis on the cardiac output of patients with congestive heart failure has been investigated by the acetylene method. Prior to the administration of digitalis, most of the subjects had subnormal values from the cardiac output.

Of twenty-two patients, three showed no improvement after the administration of the drug; ten had subjective benefit; and eight exhibited definite objective improvement. In each of the groups some of the patients showed an increase in the cardiac output per minute, some a decrease, and some no change. Consistent alterations of the cardiac output in proportion to the oxygen consumption were not observed.

AUTHOR.

Thompson, W. P., and Levine, S. A.: Systolic Gallop Rhythm: A Clinical Study. *New England J. Med.* 213: 1021, 1935.

Thirty-five patients with systolic gallop rhythm observed over a period of eleven years are reported. This number represents 16 per cent of all patients with gallop rhythm encountered during this period.

The extra sound in systolic gallop rhythm is placed in systole between the normal first and second sounds. In most cases it has a quality resembling the normal first sound. Its maximum intensity is usually in the region of the apex of the heart. Its intensity is variable in different patients and occasionally in the same patient from time to time. It may alter its intensity or even disappear with change in the position assumed by the patient, although generally it is loudest in the recumbent position. It may also appear or disappear without apparent cause.

Two-thirds of the group had no cardiovascular disease. Most of them had no complaints, having been seen in consultation because of suspected heart disease, or they presented bizarre complaints of a minor or functional nature. Most of them were "nervous" people. The remainder of the group, twelve in number, had demonstrable cardiovascular disease. Five of them had coronary artery disease, two of these and six others had arterial hypertension, usually mild in degree, and one had bundle-branch block without other evidence of cardiovascular disease. Valve defects, congestive failure or congestive signs of any sort were not found. Only two patients had cardiac enlargement. Significant electrocardiographic abnormalities were absent except in four of those with coronary disease and the one with bundle-branch block. No real incapacitation was present except in those with coronary artery disease.

Extremes of age were eleven and seventy-one years. With one exception in each group, those below forty-four years of age had no cardiovascular disease, and those above forty-four had such disease. Males were predominant in the group with cardiovascular disease, while there was no difference in the number of males and females in those without it.

None of the group is dead at the time of this report while 46 per cent of the group with diastolic gallop observed over the same period are dead. The rarity of cardiac enlargement and physical incapacitation, the slight degree of arterial hypertension in those who had it, and the complete absence of congestive signs, all point to the benignity of systolic gallop rhythm.

It appears that none of the proposed theories as to causation of the extra sound can satisfactorily account for all cases.

AUTHOR.

Nelson, H. B., and Eades, M. F.: *Some Obstetrical Aspects of Cardiac Disease Complicated by Pregnancy*. *New England J. Med.* 213: 1057, 1935.

A series of 495 patients with rheumatic heart disease complicated by pregnancy has been analyzed.

Ninety-two per cent of the cardiac failures occurred during pregnancy. Forty-seven per cent of the failures occurred in the seventh and eighth months of pregnancy. If a pregnant cardiac patient is able to go through the eighth month of pregnancy without failure, her chance of decompensation with proper care during the ninth month or during delivery should be relatively small. The authors were unable to demonstrate in this series of cases that the cardiac patient has any shorter or easier labor than the normal woman.

Sixty-seven and three-tenths per cent of these patients were delivered by the pelvic route and 32.7 per cent by abdominal route. The majority of patients in actual decompensation had abdominal deliveries. In spite of our attempts to obviate the second stage of labor, 63.4 per cent of the multiparas and 14.1 per cent of the primiparas were delivered normally, an incidence of 49.8 per cent of normal deliveries for the entire group. The low incidence of difficult pelvic deliveries is to be noted; also the increased incidence of easy artificial termination in an effort to obviate the second stage of labor. Sterilization was performed in 23.6 per cent of the cardiac cases.

In the 495 cases here studied, the mortality rate was 4.6 per cent. The incidence of mortality was little higher in patients delivered in failure than in those without. The importance of treating the pregnant cardiac patient primarily as a medical problem and secondarily as an obstetrical problem is emphasized.

AUTHOR.

Gant, J. C.: *Myxedema Heart: Report of a Case*. *New England J. Med.* 213: 918, 1935.

This report adds to the literature one more case of congestive heart failure associated with myxedema. That congestive failure was present is shown by the dyspnea and peripheral edema with the pulmonary congestion shown both by auscultation and x-ray. Part of the gross enlargement here shown is no doubt due to the dilatation usually accompanying congestive failure. In this case the picture may not be due to uncomplicated myxedema, in view of the persistent intraventricular block and rather rapid heart on only 1.5 gr. of thyroid substance. However, the fact that the patient is now active without any signs of failure suggests that myxedema is the added factor responsible for the heart failure.

Myxedema as one of the causes for auricular fibrillation is suggested by this case. This seems strange in view of the frequency of this arrhythmia in hyperthyroidism. That normal rhythm was established coincidentally with the giving of thyroid in this case is a fact worth noting. The possibility of its being a coincidental finding is recognized.

AUTHOR.

Abt, Arthur F.: *Erythema Annulare Rheumaticum*. *Am. J. M. Sc.* 190: 824, 1935.

Erythema annulare rheumaticum is exclusively associated with rheumatic endocarditis, and its appearance has been noted only in association with such cases. The occurrence of this rash in children suffering with rheumatic endocarditis, as is

the case with other cutaneous lesions found in this disease, may be considered as evidence of either the persistence of an active rheumatic endocarditis or as a sign of reactivation of the disease.

AUTHOR.

Starr, S., and Parrish, P.: Rheumatic Pleurisy, With Particular Reference to Its Demonstration by Roentgen Study. *Am. J. Dis. Child.* 50: 1187, 1935.

Routine anteroposterior and oblique views of the chest frequently demonstrate rheumatic interlobar pleurisy during the active phases of rheumatic fever.

By roentgen ray studies of an unselected series of hospitalized children, interlobar pleural thickening was demonstrated in 9 per cent of "normal" children, in 13.5 per cent of children with chorea alone, and in 43.6 per cent of children with other manifestations of rheumatic fever.

The incidence of thickened pleura in the group with rheumatic infection bears no relation to the incidence of previous pneumonia, pulmonary congestion of cardiac decompensation, or tuberculosis of childhood.

The greatest percentage of pleurisy was found to be associated with rheumatic pericarditis clinically, at autopsy, and by roentgen ray examination.

AUTHOR.

Rodrigue, Carlos, and Battro, Antonio: Aorta and Rheumatism. *Rev. argent. de cardiología.* 2: 170, 1935.

A survey of the literature suggests that there is no absolute proof of the existence of aneurysms of rheumatic origin since no anatomical-pathological control has ever been carried out. Rheumatic inflammatory reactions of the aorta have been satisfactorily demonstrated, but they are never so extensive as to cause destruction of the elastic layer.

The two observations reported here are of simultaneous aortic stenosis and regurgitation of rheumatic origin which showed obvious radiological alterations of the vascular shadow. Necropsy, on the other hand, revealed practically normal aortas in both cases. The cause of the roentgenological alterations must be interpreted as functional in character. Under these circumstances the radiological diagnosis of aneurysm and rheumatic aortitis are misinterpretations of the vascular shadow.

The authors are inclined to believe that rheumatic aortic lesions are of no great clinical importance. Aneurysms and aortitis therefore should continue to be regarded as synonymous with syphilis.

AUTHOR.

Banerjee, J. C.: Rheumatic Heart Disease in Childhood. *Indian J. Pediat.* 2: 279, 1935.

The following is a summary of the observations based on an analytical study of 25 cases of rheumatic heart disease in childhood found among 85 cases of cardiac rheumatism in a series of 256 consecutive cardiac cases seen in hospital and private practice.

Rheumatic infection was found to play an important rôle in the causation of heart disease in India. About one-third (33.2 per cent) of all cases of organic heart disease in this series had a rheumatic etiology.

Twenty-two out of 25 patients (88 per cent) were found to belong to the poorer classes.

The curve of age incidence for rheumatic heart disease began at four to six years, rose to its peak at ten to twelve years, and then declined at thirteen to fifteen years. There was a marked preponderance of males over females. A familial incidence was observed in 24 per cent of the cases.

Close inquiry revealed a history of one or more attacks of swollen or painful joints of a mild or severe type with or without fever occurring some time or other in course of the evolution of rheumatic heart disease in 19 out of 25 cases (76 per cent). A history of tonsillitis or sore throat was present in 32 per cent of cases.

Chorea was not seen in any of the cases presented here.

Subcutaneous nodules are probably not so rare as one is likely to believe. They were present in 2 cases out of 25 (8 per cent).

Active rheumatic carditis was present in 3 cases, mitral stenosis in 15 (60 per cent), aortic incompetence in 2 (8 per cent), and mitral stenosis combined with aortic incompetence in 3 (12 per cent). In one case a tentative diagnosis of aortic stenosis was made in addition to aortic incompetence and mitral stenosis.

Most of the cases (52 per cent) came under observation with moderate or marked cardiac enlargement associated with symptoms and signs of congestive failure.

Relapses were found to occur in 40 per cent of cases as compared with 70 per cent in the West.

In treatment absolute rest in bed was considered to be most essential. Salicylates in large doses with double the dose of sodium bicarbonate were found to be successful in relieving joint pains and in reducing the course of the febrile attack. Digitalis with ammonium chloride was found to be of great value in cases of congestive failure. The sedimentation rate of the erythrocytes was considered to be very helpful in deciding how long a patient with a rheumatic heart should be kept under strict bed rest.

The mortality of the cases in this series was 4 per cent in two years and 24 per cent in ten years from the onset of the illness.

AUTHOR.

Coburn, Alvin F., and Pauli, Ruth H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process. IV. Characteristics of Strains of Hemolytic *Streptococcus*, Effective and Non-Effective, in Initiating Rheumatic Activity. *J. Clin. Investigation* 14: 755, 1935.

The biological characteristics of strains of hemolytic streptococcus associated with acute pharyngitis in rheumatic subjects have been studied.

Half of the strains selected initiated intense activity of the rheumatic process and the other half failed to initiate rheumatic activity in susceptible subjects.

The cultural characteristics of the organisms studied were essentially the same in both groups. All strains were of human type.

The effective organisms were characterized by the capacity to produce strong skin toxins and streptolysins and were indistinguishable from scarlatinal strains of *Streptococcus hemolyticus*. They gave rise to the development of high titers of antistreptolysin in the subjects infected.

Those strains which failed to produce skin toxin and streptolysin, and did not give rise to the development of high titers of antistreptolysin, were ineffective in activating the rheumatic process.

AUTHOR.

Coburn, A. F., and Pauli, R. H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process. V. Active and Passive Immunization to Hemolytic *Streptococcus* in Relation to the Rheumatic Process. *J. Clin. Investigation* 14: 763, 1935.

Active immunization with streptococcus toxin neither prevents streptococcus infection nor inhibits the development of the rheumatic process.

The introduction of protective antibodies just prior to the expected attack does not decrease and may possibly increase the intensity of the rheumatic recrudescence.

The development of rheumatic activity appears to depend not only upon infection with a toxin-producing strain of hemolytic streptococci, but also upon the host's immune response to this infection. AUTHOR.

Coburn, A. F., and Pauli, R. H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process. VI. The Significance of the Rise of Antistreptolysin Level in the Development of Rheumatic Activity. *J. Clin. Investigation* 14: 769, 1935.

The median of the antistreptolysin determinations on 176 individuals in good health was 71 units. This is somewhat higher than the natural human level of 50 units.

The median titer developed in acute rheumatism was 500 units, and the geometric mean 490 units. In most instances the titer returned to approximately natural level within a period of one year.

The onset of acute rheumatism coincided with a sharp rise in antistreptolysin titer.

Rheumatic patients infected with hemolytic streptococcus who escaped recrudescence showed little or no change in antistreptolysin titer.

The relation of the immune response of the host to the development of rheumatic activity is discussed. AUTHOR.

Coburn, A. F., and Pauli, Ruth H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process. VII. Splenectomy in Relation to the Development of Rheumatic Activity. *J. Clin. Investigation* 14: 783, 1935.

Splenectomy did not permanently modify either the immune response or the character of the rheumatic recrudescence.

Nine out of twenty apparently quiescent rheumatic subjects developed recrudescences as a direct sequel to splenectomy.

All of these nine individuals had elevated antistreptolysin titers at the time of operation, and none of them showed any increase in titer during or after the recrudescence.

This shows that following operative manipulation of antibody-producing tissue during subsiding rheumatism, an exacerbation of symptoms may develop in the absence of further rise in antistreptolysin titer. AUTHOR.

Moore, A. G.: Incidence of Cardiac Diseases. *J. Indiana M. A.* 28: 419, 1935.

It was found that 77.7 per cent of the cardiovascular abnormalities were in the hypertensive group. The author believes the increased nervous tension of today is responsible for the constantly increasing cases in this group. The study shows that individuals with hypertension have a little longer span of life than those in the valvular or nonhypertensive group.

Primary occurrences of cases in the valvular group, especially in the earlier age findings, are probably due to intercurrent infections. Palpable arteriosclerosis becomes established five years earlier in the hypertensive group than in the non-hypertensive group, but following this, it is increased in practically the same ratio for both groups.

Lewis, Thomas: The Manner in Which Necrosis Arises in the Fowl's Comb Under Ergot Poisoning. *Clin. Sc.* 2: 43, 1935.

The poison ergotoxine constricts the arteries of the comb; this constriction is one that cannot be released by relaxation of vasomotor tone or by local warming. The constriction is maintained if ergot injections are repeated day by day, but it is insufficient to stop the blood flow through the comb, which continues a little

warmer than the surrounding atmosphere and shows at first no signs of desiccation. About the third or fourth day the nutrition of the walls of the vessels begins to suffer, for about this time stasis occurs in them, the blood in the capillaries being in a state rendering its dislodgment difficult.

Ergot produces its ultimate effects entirely through arterial spasm; a direct poisoning of the tissues seems to play no part. The vasoconstriction does not lead directly to tissue necrosis but to damage to the walls of the vessels resulting in dilatation, and in stasis or thrombosis, either of which will bring the circulation locally to an end and together determine dry necrosis.

E. A.

Katz, L. N., Lindner, E., and Landt, H.: On the Nature of the Substance (S) Producing Pain in Contracting Skeletal Muscle: Its Bearing on the Problems of Angina Pectoris and Intermittent Claudication. *J. Clin. Investigation* 14: 807, 1935.

The main findings in this study with regard to the amount of exercise required to cause pain and fatigue in the muscles of the arms of normal subjects are:

a. Circulatory slowing caused a decrease in the amount of exercise required to cause pain, the effect being disproportionately greater at high degrees of circulatory slowing. The amount of blood trapped in the arm played an insignificant rôle. Circulatory slowing had its greatest effect at the fastest rates of exercise.

b. Increasing the rate of exercise led to a decrease in the amount of exercise required to cause pain when the circulation to the limb was unobstructed. Slowing the circulation led to a diminution of this effect of rate of exercise. This effect of rate of exercise disappeared when the circulation in the limb was stopped.

c. Exercise of a large group of muscles of the leg to the point of pain had a twofold action on the amount of exercise required to cause pain in a subsequent arm exercise; viz., (1) by an action on the central nervous system it augmented the amount of exercise required to cause pain, and (2) by an action through transport of blood from the exercised legs to the muscles of the arm it decreased the amount of exercise required to cause pain. Special procedures were required to separate these two effects.

d. Increasing the CO₂ content of the blood in the arm decreased the amount of exercise required to cause pain. Ingestion of large amounts of sodium bicarbonate increased the amount of exercise required to cause pain. Ingestion of sodium bicarbonate also tended to alleviate the pain of patients with intermittent claudication and those with angina pectoris.

e. In right-handed subjects less exercise was required to cause pain in the left than in the right arm.

f. The effects of these procedures on neuromuscular fatigue were not related quantitatively to their effects on pain. With certain procedures, such as the ingestion of sodium bicarbonate, the effects were opposite.

The significance of these results on pain and fatigue in muscle is discussed in the body of the paper. The salient conclusions from these experiments are:

a. The time allowed for recovery between contractions in a rhythmically contracting muscle alters the rate of accumulation of the substance (s) leading to pain, implying that the pain-producing substance (s) is a product of metabolic muscular activity.

b. The substance (s) causing pain diffuses into and out of the blood stream. It is nonvolatile since it operates even after passing through the lungs.

c. The appearance of pain in muscle is dependent not only upon the local production of pain-producing substance (s) but to a certain extent upon the transport of such a substance (s) from other regions.

d. This nonvolatile pain-producing substance (s) appears to be acid in character; at least its action is facilitated by acid and retarded by alkaline substances.

e. Acids and bases exhibit summation of effect with the pain-producing substance (s) by changing the pH of the end-organs, by altering the buffering capacity of the muscle concerned.

f. Training tends to lessen the action of the pain-producing substance (s) probably by altering the buffering capacity of the muscle concerned.

g. The variability in the appearance of fatigue, which is independent of pain, plays an important rôle in forestalling the appearance of pain under certain circumstances.

The bearing of these findings on the appearance of pain in angina pectoris and in intermittent claudication is discussed at the end of each section.

AUTHOR.

Grant, R. T.: A Portable Thermo-electric Couple for Measuring Skin Temperature. *Guy's Hosp. Rep.* 85: 209, 1935.

The apparatus described by Grant is a modification of that developed by Sir Thomas Lewis, in which the circuit has been simplified. A sensitive, but robust, pointer galvanometer is used instead of the mirror instrument, and temperatures are read directly from the galvanometer scale. It has proved serviceable in studying disturbances of the peripheral circulation at the bedside.

L. H. H.

Harris, R. I.: The Rôle of Sympathectomy in the Treatment of Peripheral Vascular Disease. *Brit. J. Surg.* 23: 414, 1935.

Significant improvement in symptoms and course of Buerger's disease was obtained in 79 per cent of 24 cases subjected to lumbar sympathectomy (21 cases) and stellate ganglionectomy (3 cases).

In this disease Harris believes that a good result of operation can be predicted if one obtains a preoperative definite rise of skin temperature under spinal anesthesia or nerve block.

In peripheral arteriosclerosis the number of cases in which vasospasm is a factor warranting the risk of this operation is small. In five of twelve such cases, appreciable benefit was obtained, which has lasted sufficiently long to justify the operation. Four cases of Raynaud's disease so treated were improved.

An operative technic is given.

L. H. H.

Baena, V.: Determination of the Circulating Blood Volume With a Spectrophotometric Method. *Ztschr. f. d. ges. exper. Med.* 96: 420, 1935.

A modification of Haldane's carbon-monoxide method, using Bechstein's spectrophotometer instead of a calorimeter, was used. The spectrophotometer appears more reliable and accurate than the calorimeter in determining the amount of carbon-monoxide hemoglobin and circulating blood volume.

In experimenting with rabbits, the volume of circulating blood determined by this method was found to be one-fourteenth of the body weight. Injection of thyroxin increased the volume of circulating blood, whereas ice bags applied to the body to activate the thermo-regulating mechanism produced no change.

J. K.

Irving, Lawrence, and Welch, Mary Scott: The Effect of the Composition of the Inspired Air on the Circulation Through the Brain. *Quart. J. Exper. Physiol.* 25: 121, 1935.

The flow of blood through the femoral vein and longitudinal sinus of the dog was examined by comparison of the A-V oxygen differences. Inhalation of 10

per cent carbon dioxide in oxygen increased blood flow through the brain of anesthetized dogs to the estimated extent of from two to four times. At the same time flow through the hind leg was diminished often to less than half the normal rate. These vascular changes indicate a differential vascular control giving preferential consideration to the brain. The stimulus for differential control may originate in the brain itself, but the result may be reinforced by, or it may even originate in, a site extrinsic to the tissue.

E. A.

Allen, Edgar V., and Ghormley, R. K.: *Lymphedema of the Extremities: Etiology, Classification and Treatment; Report of 300 Cases.* Ann. Int. Med. 9: 516, 1935.

Three hundred cases of lymphedema are classified clinically in two main groups depending upon the presence or absence of clinical evidence of infection. Noninflammatory lymphedema is of the primary or secondary type; under the former classification are considered lymphedema praecox and congenital lymphedema and under the latter classification are considered lymphedemas due to occlusion of lymph nodes. Inflammatory lymphedema is considered under the heading of primary and secondary inflammatory lymphedema depending upon whether the inflammation arises spontaneously or whether it is secondary to venous stasis, trichophytosis, and so forth. The various clinical types of lymphedema present widely diverse clinical manifestations, but the symptoms and development of each type are characteristic within rather narrow boundaries. The clinical classification is not supported by pathological studies as only congenital lymphedema is characteristic pathologically.

Lymphedema in man results from multiple causes, but the mechanism of its productions appears to be the same in all cases. Lymph stasis occurs as a result of lymphatic obstruction; the intralymphatic pressure increases and causes dilatation of lymph vessels with consequent insufficiency of valves and further lymph stasis. The protein content of lymph increases and fibroblasts proliferate rapidly and cause fibrosis. As a result of an increased quantity of lymph in the tissues, inflammation may occur producing lymphatic thrombosis and further stasis. The cycle, which is a vicious one, consists of lymph stasis, fibrosis, inflammation with further stasis and more fibrosis. Medical treatment consists in prevention of lymph stasis by adequate bandaging of the limbs. If this is done, there will be no progressive enlargement of the limb due to fibrosis. Surgical treatment is an attempt to correct the consequences of inadequate medical supervision. The Kondoleon operation is the most satisfactory; it is viewed solely as a plastic procedure whereby hypertrophied skin and subcutaneous tissues are removed. The results, while fairly good, are not entirely satisfactory.

AUTHOR.

Dandy, Walter E.: *The Treatment of Carotid Cavernous Arteriovenous Aneurysms.* Ann. Surg. 102: 916, 1935.

Arteriovenous aneurysms of the type indicated are more common than arteriovenous fistulas in any other part of the body. About three-fourths of the fistulas are traumatic; the others occur spontaneously as a result of congenital or acquired aneurysms. The clinical syndrome consists of exophthalmos, pulsation of the protruding eye, and a subjective roar which to auscultation is a systolic murmur. Cure is not dependent upon isolation of the aneurysm by occlusion of the carotid, but by thrombosis in the fistula, the carotid artery or venous tributaries. In each of two instances in which arterial ligations had not cured the fistulas, a silver clip was placed upon the intracranial portion of the internal carotid artery. In one case

there was immediate and complete cure; in the other case it was necessary to excise most of the collateral branches entering the ophthalmic artery to complete the cure.

E. A.

Seupham, G. W., and de Takáts, G.: *Peripheral Vascular Diseases. A Review of Some of the Recent Literature With a Critical Review of Surgical Treatment.* Arch. Int. Med. 56: 530, 1935.

The review is in two parts; the first, an excellent presentation of the salient features of the many recent advances in the general field of the peripheral circulation; the second, a surgeon's critical summary of most of the surgical aspects of treatment.

By far the greater part of the work reviewed has been done in the past five years; its extent is indicated by the use of 90 pages of the journal for an exceedingly meaty consideration of some 260 articles.

In the field of the physiology of the peripheral circulation Sir Thomas Lewis is being followed by several able investigators. Most important advances have been made in the field of conservative therapy based on new physiological discoveries. Furthermore, as the various disorders are better understood and are diagnosed earlier, much of the previous therapy is being discarded. The operation of periarterial sympathectomy, for instance, is being limited much more strictly than in the early days of enthusiasm. The etiology of Buerger's disease remains unsolved, but its early recognition and treatment are aided by recent investigation.

L. H. H.

Liu, A. C., and Rosenblueth, A.: *Reflex Liberation of Circulating Sympathin.* Am. J. Physiol. 113: 555, 1935.

Direct stimulation of sympathetic nerves leads to the passage into the blood of sympathin, a sympathomimetic substance the presence of which may be demonstrated by reactions of adequate denervated autonomic effectors. The question arises, Can reflex activation of sympathetic nerves cause sympathin to pass into the blood? Controlled experiments on cats show that stimulation of the sciatic or one of the brachial nerves causes contraction of the nictating membrane, a manifestation of circulating sympathin under conditions of the experiment. While sympathin originates from sympathetic nerves, its presence in the blood in the experiments did not depend upon certain parts of the sympathetic nervous system, as contractions of the nictating membrane occurred when the thoracic sympathetics were present and the cephalic and abdominal sympathetics were absent, as well as when conditions were reverse. It appears that sympathin may play a rôle as a hormone in certain physiological conditions.

E. A.

Ash, Rachel: *Use of Typhoid Vaccine in Treatment of Chorea: Its Possible Dangers.* Am. J. Dis. Child. 50: 879, 1935.

Intravenous injections of typhoid vaccine may be of harm in the presence of carditis.

During the febrile reaction following intravenous injections of typhoid vaccine, there is a depression of granulocytes. This method of therapy should be checked by frequent determinations of the white blood cell count.

Typhoid vaccine therapy does not prevent a recurrence of chorea.

Book Review

ELEKTROKARDIOGRAPHISCHE BEFUNDE BEI HERZINFARKT. By Doctor Anton Jervell. Acta Medica Scandinavica, Supplementum LXVIII, Kristes Boktrykkeri, Oslo, 1935.

This monograph, in German, is devoted to the description and classification of the electrocardiographic findings in sixty-five cases of myocardial infarction. The cases were not selected; all the cases observed during the period of the study in which a clinical diagnosis of myocardial infarction was made are included. In addition to the standard leads, a precordial lead from the region of the apex was taken in more than one-half the cases (thirty-six). In taking this lead the galvanometer connections were so arranged that negativity of the exploring electrode was represented by a downward, instead of by an upward, deflection, and the indifferent electrode was placed on the back. Serial electrocardiograms were taken in the great majority of the cases, and twenty-six of the patients studied came to autopsy. The case histories are given in an appendix. The illustrations include reproductions of the initial and some of the subsequent electrocardiograms in each case, and also sketches showing the location of the infarct when this was determined by autopsy.

Extrasystoles were observed in thirty-four cases, auricular flutter or fibrillation in seven, auricular paroxysmal tachycardia in one, atrioventricular heart-block in three, prolonged conduction time in three, sino-auricular block in one, and dissociation with interference in one. The ventricular complex was abnormal in all cases. Bundle-branch block of the common type was present in seven cases, bundle-branch block of the uncommon type in one, arborization block in five, small complexes without intraventricular block in fourteen, large Q-waves in Lead III in nineteen, and large Q-waves in Lead I in five.

Displacement of the RS-T segment (1 to 8 mm.) was observed in most instances in which the patient came under observation shortly after the coronary accident, but was not always maximal in the first curve taken. It persisted longer in the precordial lead than in the standard leads. Progressive T-wave changes occurred both in those cases which showed RS-T displacement and in those which did not. The T-wave changes reached their height in from two weeks to three months after the beginning of infarction. In thirty-five cases the T-wave changes were of the T_1 type; in twenty-six cases they were of the T_2 type. Changes in the RS-T segment and in T were the most valuable as an aid in diagnosis; they occurred in forty-nine of the sixty-five cases. The precordial lead was found invaluable and showed characteristic changes in twenty-six of the thirty-six cases in which it was used. It showed such changes in all but one of the twenty-one cases in which the standard curves were of the T_1 type and in five of the twelve cases in which the standard curves were of the T_2 type.

Arborization block appeared to be of serious prognostic import, but the other electrocardiographic abnormalities did not seem to be of any help in foretelling the outcome. In sixteen of the twenty-six cases which came to autopsy, the infarct involved the anterior wall of the heart; in the remaining ten it involved the posterior wall. In eleven of the cases in which the infarct was anterior, the standard leads were of the T_1 type; in three cases arborization block was present, and in the remaining two cases the standard leads could not be classified as be-

longing either to the T_1 or to the T_2 class. In all of the ten cases in which the infarct was posterior, the standard leads showed changes of the T_2 type. It is suggested that changes of the T_1 type are sometimes absent when the infarct is anterior because anterior infarcts frequently extend to the apical portions of the posterior wall.

The author was able in the case of very thin normal subjects to produce inversion of the T deflection in the precordial lead employed by placing an ice bag over the heart for a half hour or longer.

This monograph is a very valuable contribution to our knowledge of the electrocardiographic changes produced by myocardial infarction. It is particularly valuable because it deals with a comparatively large series of unselected cases and because of the large number of autopsies obtained. It is very well written and profusely illustrated. The list of references includes all of the more important and many of the less important papers dealing with the electrocardiogram in myocardial infarction which have appeared either in America or in Europe.

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DIASTOLIC GALLOP RHYTHM

A NOTE ON CERTAIN FACTORS INFLUENCING PROGNOSIS*†

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THE grave prognostic significance of diastolic gallop rhythm of the heart sounds is well known. A study of 89 cases, however, has shown some differences in prognosis according to simple findings easily made at the bedside. We propose to present such factors as may be of some aid in predicting the prognosis of the individual patient and shall not attempt to include all such factors or those which have been adequately emphasized previously.

All of the patients in this series were seen in the private practice of one of us during the past twelve years. Auscultation was the only means used for the detection of the gallop sound. We have made no attempt to separate protodiastolic, mesodiastolic, and presystolic gallop rhythm for the purposes of this study because of the uncertainty entailed in the proper classification of these forms clinically. We are given support for this apparent neglect in the recent work of Wolferth and Margolies,¹ who have shown by electrophonocardiographic studies that gallop sounds protodiastolic in origin may actually be closer to the normal first sound than to the second and that sounds presystolic in origin may be closer to the second sound. This apparent displacement of the extra sound is, of course, a function of cardiac rate. Since diastolic gallop rhythm occurs relatively infrequently at slow rates, we believe the clinical classification of the various forms to be usually impracticable if not often wholly erroneous.

Only patients who were known to be dead and the duration of whose lives after the detection of gallop rhythm was known to us were selected. There was a total of 192 patients in whom diastolic gallop

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†Aided by a grant from the Proctor Fund of Harvard University for the Study of Chronic Diseases.

rhythm was observed during the twelve years. Ninety, or 47 per cent, are known to be dead. The duration of life was known to us in 89 cases. The average life for these was ten months and twenty days. The remainder were either still alive, or follow-up data regarding them were not available. A review of the present clinical condition of those we know to be still living led us to believe that the figures we shall present would have been somewhat altered if the entire group had been followed until death. A lengthening of the duration of life after the detection of gallop rhythm would probably result because of the inclusion of a few patients who had no organic heart disease (a normal third heart sound resembling gallop rhythm) and some patients with acute rheumatic carditis with delayed auriculoventricular conduction time who often have a satisfactory prognosis.

General Considerations.—All of the eighty-nine patients had organic cardiovascular disease. Seventy-six per cent were males; 24 per cent were females. There were only seven patients under forty years of age and only eight seventy years old or older. The youngest was ten years old; the oldest was seventy-five. Coronary artery disease was predominant etiologically, making up 52 per cent of the series. About two-thirds of these had coronary occlusions. Thirty-eight per cent

TABLE I

	NUMBER OF CASES	AVERAGE DURATION OF LIFE		
		YEARS	MONTHS	DAYS
Total cases -----	89	0	10	20
Hypertensive cardiovascular disease -----	34	0	11	22
Coronary artery disease (including angina pectoris) -----	46	0	10	15
Without coronary occlusion -----	16	1	3	17
With coronary occlusion -----	30	0	7	24
Gallop appearing during acute infarction -----	14	0	4	29
Rheumatic heart disease -----	6	0	1	28
Etiology unknown -----	3	1	0	15
Age: Below 40 years -----	7	0	2	24
40 to 49 years -----	17	0	8	14
50 to 59 years -----	30	0	10	29
60 to 69 years -----	27	0	9	25
70 years and over -----	8	1	11	25
Sex: Males -----	68	0	10	19
Females -----	21	0	10	21
Total with hypertension -----	63	1	0	15
Total without hypertension -----	23	0	6	3
Systolic blood pressure: Below 120 mm. -----	10	0	0	22
120 to 149 mm. -----	18	0	9	7
150 to 199 mm. -----	34	1	1	25
200 mm. and above -----	24	0	11	27
Diastolic blood pressure: Below 90 mm. -----	20	0	5	11
90 to 99 mm. -----	13	1	8	0
100 to 119 mm. -----	27	1	0	10
120 mm. and above -----	26	0	8	23
Frank congestive failure -----	38	0	6	17
Without congestive failure -----	51	1	0	14
Intraventricular heart-block -----	16	1	5	8
Normal intraventricular conduction -----	30	0	11	23

had hypertensive cardiovascular disease. Arterial hypertension was common in the other etiological groups, so that a total of 71 per cent of the entire series had abnormally elevated blood pressures. Only six patients had rheumatic heart disease, none of whom had mitral stenosis. These divisions accounted for all but three patients the etiology of whose disease is unknown. The heart was clinically enlarged in 87 per cent. Forty-three per cent had frank congestive failure at the time gallop rhythm was first detected. A number of the

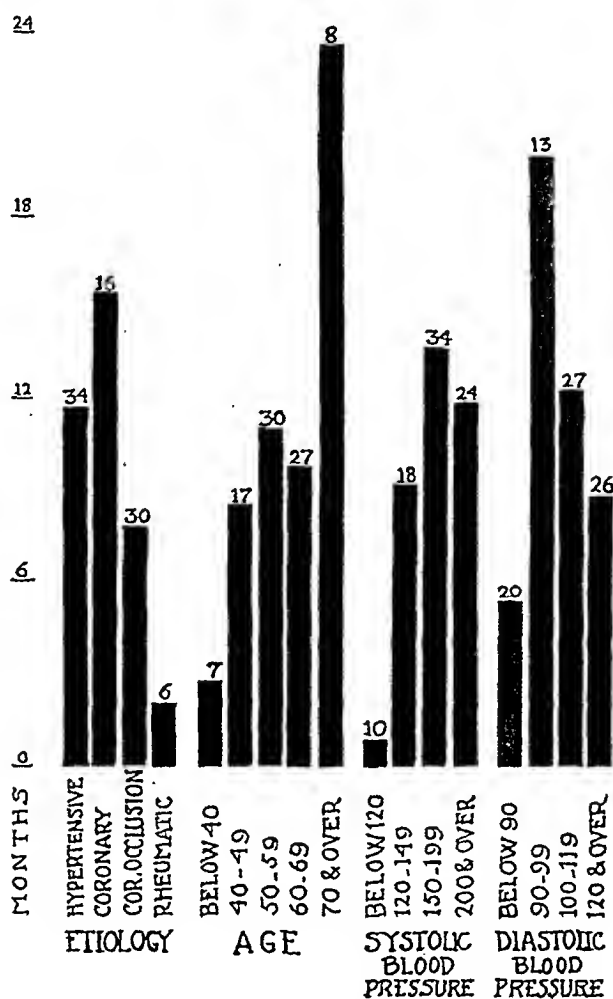


Fig. 1.—The figures at the top of each column indicate the number of patients represented.

others developed failure later. Symptoms of myocardial insufficiency were marked in the group as a whole. Normal sinus rhythm was present in every instance.

Relation of Etiology to Prognosis.—There was little difference in the length of life after detection of diastolic gallop according to the etiological diagnosis, except in the group with rheumatic heart disease. These lived an average of only about two months, a very much shorter time than either of the other two groups. This group is too small, however, to have the figures conclusive. These and the other data are shown in Table I and Fig. 1.

Coronary Occlusion.—The patients with coronary artery disease who had never suffered an occlusion at the time diastolic gallop was first detected lived about twice as long as those who had suffered an occlusion at some time, either in the past or recently. If the gallop appeared during the course of an acute myocardial infarction, the average length of life was very short. The figures in this particular, as given in the table, do not tell all the facts, however. There were fourteen patients whose gallop sounds appeared during acute infarction. Only three of these lived longer than six weeks. One lived three months. One was a physician whose gallop appeared the day following a coronary occlusion. It had disappeared by the next day and was not heard again. He made an excellent recovery and returned to active practice. More than four years later the gallop rhythm was heard again, and in another month he was dead. The third patient in this group lived twenty-one months, but since he was seen only once, it is not known whether the gallop disappeared. Another patient not included in this series had an occlusion over four years before, during the course of which gallop appeared. It disappeared, he made a good recovery, and he is still living and in good health. It would seem, then, that when gallop rhythm appears during the course of an acute myocardial infarction, the prognosis is exceedingly poor but that disappearance of the gallop is a favorable sign.

Age.—The patients who were under forty years of age at the time gallop rhythm was discovered lived on the average only about three months. Those who were seventy years or more of age averaged about two years of life. Between these extremes, i.e., between forty and seventy years, there was no significant difference in the duration of life or difference from the general average. Because of the fact that most of the patients with gallop rhythm were between forty and seventy years of age, these figures have no particular significance in the majority of patients. They are of importance, however, in the younger patients, in whom the prognosis was particularly bad, and in the older ones, in whom it was particularly good as compared to the general average.

Sex.—The duration of life in the males and in the females in this series was practically identical.

Blood Pressure.—The patients with arterial hypertension lived approximately twice as long as did those without it. Those with low systolic pressures, below 120 mm., lived on the average less than one month. With rising systolic pressure the averages became much better, particularly after a level of 150 mm. was reached. When the patients are grouped according to their diastolic pressures, a more

striking difference is seen. Those with diastolic pressures below 90 mm. lived less than six months, while those with pressures between 90 and 99 mm. lived an average of twenty months. When the diastolic pressure was elevated to figures of 100 mm. or more, the average fell considerably. Elevated systolic tensions and slightly elevated diastolic tensions were then favorable prognostic signs, on comparison with the rest of the series, while a systolic tension of less than 120 mm. was a particularly unfavorable sign. Giroux² has intimated that gallop rhythm in the presence of hypotension bears a somber prognosis, particularly in the chronic myocardial diseases.

Congestive Failure.—The patients who were in a state of frank congestive failure at the time gallop rhythm was first detected lived on the average about six and one-half months, while those who had never been in failure lived almost twice as long. This may seem an unreasonable comparison because of the obviously poorer prognosis in the patient whose heart has failed, but the fact remains that the presence of congestive signs increased the gravity of this physical sign. Many of the patients who were grouped as having no failure, of course, did develop failure later, but our attempt was made to predict the future of the individual patient at the time gallop rhythm was first observed. White³ has also mentioned the grave prognosis when heart failure is responsible for the gallop.

Intraventricular Heart-Block.—The presence of intraventricular block, in most cases typical left bundle-branch block, did not have the unfavorable influence on prognosis which might have been expected. In fact, those with such a conduction defect actually lived about 50 per cent longer than those known not to have it, and over 60 per cent longer than the general average. Defective intraventricular conduction was, then, actually a favorable finding. Eppinger and Levine⁴ found the same favorable effect of intraventricular block in a series of patients with angina pectoris.

SUMMARY AND CONCLUSIONS

The average duration of life in eighty-nine patients after the detection of diastolic gallop rhythm was ten months and twenty days. Certain easily detectable bedside findings which appeared to alter this prognosis have been studied.

Although there were but a few patients with rheumatic heart disease, the duration of life in them was markedly shorter than when some other etiology was responsible.

Gallop rhythm occurring during the early hours or days following an acute coronary closure had an extremely bad prognostic significance. Its subsequent disappearance, however, was a favorable sign.

Diastolic gallop in patients under forty years of age had a particularly ominous significance, while in patients of seventy or more years the prognosis was relatively good.

The sex of the patient seemed to have no bearing on the duration of life.

The prognosis was poorer in patients without hypertension than in those with it, particularly if the systolic tension was below 120 mm.

The patients with congestive failure at the time gallop was first found lived about half as long, on the average, as those who had not had failure.

The existence of intraventricular heart-block not only did not make the prognosis worse but actually seemed to make it more favorable.

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PULSUS ALTERNANS.

A NOTE ON CERTAIN FACTORS INFLUENCING PROGNOSIS*†

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SEVERAL factors which have a bearing on the duration of life of patients with alternation of the pulse have come to our attention. It has been abundantly confirmed in an extensive literature that pulsus alternans is an ominous sign and that the patient with it will generally not live more than a few years. This was well demonstrated some time ago by Mackenzie¹ and by Windle.² We have noticed several factors, easily detectable at the bedside, which influenced the duration of life in our cases and which may allow us somewhat greater accuracy in predicting the outcome for the individual patient. We shall make no attempt to discuss all the factors concerned. We wish only to present some which have not been mentioned or have been inadequately emphasized in the literature.

All of the patients reported here were seen in the private practice of one of us. The alternation was detected by means of the sphygmomanometer, and all cases were constant in type, as contrasted to alternation which occurs for but a few cycles following premature contractions. There were no cases of pseudo-alternation due to bigeminy.

One hundred seventeen patients with alternation have been observed during the past twelve years. This study will be confined to the seventy-one who are known to be dead and the dates of whose deaths are known to us. The others are either still alive or the eventual outcome is unknown. A study of their records led us to believe that the figures to be presented would not have been materially changed if the entire series of 117 had been followed to death. It is obvious that pulsus alternans of the type that occurs only during a paroxysm of tachycardia is not included in this study. One such patient who had typical alternation observed in 1914, when the heart rate was 250, is alive and well today without any cardiac disability.

General Aspects of the Group.—All of the seventy-one patients had organic cardiovascular disease. Hypertensive cardiovascular disease and coronary artery disease were equally represented. The entire series fell into these two groups with the exception of six patients with rheumatic heart disease and two the etiology of which was unknown.

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†Aided by a grant from the Proctor Fund of Harvard University for the Study of Chronic Diseases.

Arterial hypertension existed in 81 per cent of those with coronary disease and in two of those with rheumatic heart disease, making a total of 83 per cent with arterial hypertension. The heart was clinically enlarged in 77 per cent. Symptoms and signs of myocardial insufficiency to a fairly marked degree were present in the majority. The functional state of the group as a whole was remarkably poor. The average duration of life after the detection of pulsus alternans was fourteen and one-half months.

Effect of Age.—Since the occurrence of alternation in young individuals is rare, it is not surprising that only five patients were under the age of forty years. In these the average duration of life after detection of the alternating pulse was about six months, less than half the general average. Patients at the other extreme of age, those of seventy years or more, lived almost nineteen months, three times as long as the youngest group, and considerably longer than the general average. Between these extremes there was a gradual increase in the length of life. The older the patient at the time alternation was detected, the longer the duration of life after detection. These and the other data are shown in Table I and Fig. 1.

TABLE I

	NUMBER OF CASES	AVERAGE DURATION OF LIFE		
		YEARS	MONTHS	DAYS
Total cases -----	71	1	2	13
Hypertensive cardiovascular disease -----	32	1	4	23
Coronary artery disease (including angina pectoris) -----	31	—	—	—
With coronary occlusion -----	9	0	5	19
Without coronary occlusion -----	22	1	5	13
Alternation appearing during acute infarction -----	5	0	1	15
Rheumatic heart disease -----	6	0	9	6
Unknown etiology -----	2	0	0	27
Age: Below 40 years -----	5	0	6	4
40 to 49 years -----	10	0	10	18
50 to 59 years -----	24	1	3	28
60 to 69 years -----	24	1	2	27
70 years or more -----	8	1	6	24
Sex: Males -----	50	1	4	29
Females -----	21	0	8	17
Total with hypertension -----	59	1	3	13
Total without hypertension -----	12	0	8	24
Systolic blood pressure: Below 120 mm. -----	4	0	1	6
120 to 149 mm. -----	16	1	0	2
150 to 199 mm. -----	21	1	10	15
200 mm. and above -----	30	0	11	27
Diastolic blood pressure: Below 90 mm. -----	8	0	10	9
90 to 99 mm. -----	9	2	2	7
100 to 119 mm. -----	26	1	6	3
120 mm. and above -----	28	0	7	27
Frank congestive failure -----	25	0	10	11
Without congestive failure -----	46	1	4	21
Intraventricular heart-block -----	14	2	2	10
Normal intraventricular conduction -----	19	1	4	13

Sex.—The average life, after discovery of pulsus alternans, of the fifty males was about seventeen months; of the twenty-one females, eight and one-half months. The prognosis, then, seemed to be twice as poor in females as in males.

Blood Pressure.—The average length of life after detection of pulsus alternans in the patients with arterial hypertension was fifteen and one-half months, while in those without it it was nine months. These figures became more striking when the blood pressure groups were

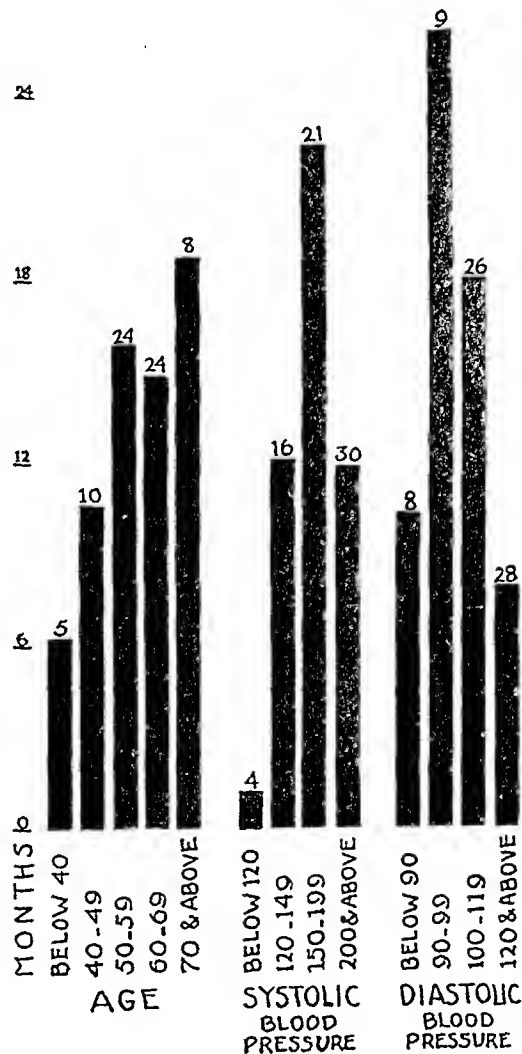


Fig. 1.—The figures at the top of each column indicate the number of cases represented.

more closely analyzed. There were four patients with systolic tensions below 120 mm. The average length of life in these was only slightly more than one month. The group with normal pressures of 120 to 149 mm. averaged one year of life. With a moderate elevation to 150 to 199 mm. the average was strikingly longer, almost twice as long as was the general average. With still higher tensions of 200 mm. or more the average fell again to about one year. The average length of life of patients with normal diastolic tensions was somewhat

shorter than that of the group as a whole. The same is true of those with markedly elevated tensions. Those with a slight elevation to 90 to 99 mm. lived almost twice as long as the general average, those with moderate elevations considerably longer than the general average. Here we find that the higher the pressure, either systolic or diastolic, the better the prognosis until very high pressures were reached, when the averages fell again. Because of the very great frequency of hypertension in patients with pulsus alternans, this relationship becomes important. Hewlett³ has stated that the outlook in patients with alternation is better if the blood pressure is high. This is true according to our series until the pressure becomes very high.

Congestive Failure.—Patients with frank congestive failure at the time alternation was first found made up 35 per cent of the series. The average duration of life in them was about ten and one-half months. The remainder presented no congestive signs or only a few minor ones. These latter lived, on the average, about 60 per cent longer than did those with failure. A number of the patients grouped as having no failure did have failure later, but the contrast was made according to the findings at the time alternation was discovered. In some respects this was scarcely a fair comparison, since the prognosis in a patient with frank congestive failure, other things being equal, would obviously have been worse than in one without it, regardless of the presence of pulsus alternans. The fact remains, nevertheless, that the presence of congestive failure increased the gravity of this physical sign.

Coronary Artery Disease.—The patients with coronary artery disease without occlusion who developed alternation of the pulse lived an average of seventeen and one-half months, while those who had suffered occlusions lived but five and one-half months. Those who had alternation during the early hours or days following an acute coronary closure lived even a shorter time—one month and a half. While the prognosis in coronary disease is known to be variable, these figures indicate a much more rapid course when alternation is present than is generally the case without it. It is our impression that on more careful study pulsus alternans will be found to occur during the early days following acute coronary thrombosis and then be seen to disappear with recovery and that the patients in whom this happens may yet have a more favorable prognosis.

Intraventricular Heart-Block.—There were fourteen patients with defective intraventricular conduction among the thirty-three whose electrocardiograms were taken. These, after alternation appeared, lived more than 50 per cent longer than those known not to have such conduction defects. Intraventricular block, then, not only did not

increase the gravity of the entire picture, but actually seemed to make the outlook somewhat better. This same favorable influence of intraventricular block was shown by Eppinger and Levine⁴ in a series of patients with angina pectoris.

SUMMARY AND CONCLUSIONS

Certain factors which seemed to have a bearing on the prognostic significance of pulsus alternans in a series of 71 patients have been analyzed. Only patients known to be dead were selected for this study. The average duration of life after the detection of alternation was fourteen and one-half months.

The younger the patient the worse the prognosis was found to be.

The subsequent duration of life in the males was twice that in the females.

Moderate elevation of either the systolic or diastolic blood pressure seemed to exert a protective influence, but the prognosis became worse again when the pressure was very high.

The prognosis was considerably worse when congestive failure was present at the time of detection of alternation than when it was absent.

The occurrence of pulsus alternans in coronary occlusion, particularly if it appeared during the early hours or days following an acute myocardial infarction, seemed to make the prognosis much more grave.

The patients with intraventricular heart-block lived longer by more than 50 per cent than did those without it.

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A CASE OF PARASYSTOLE SHEWING SIMPLE INTERFERENCE DISSOCIATION

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INTRODUCTION

ALTHOUGH normally the sino-auricular node acts as the pacemaker for the whole heart, governing the auricular rate and through the conducting tracts controlling the ventricles, instances are frequent in which the authority of the normal pacemaker is, as it were, called in question. One is familiar with the paroxysmal tachycardias, in which the cardiac rhythm is dominated by an ectopic centre emitting impulses at a high rate, against which the sinus rhythm is ineffective. Again, in conditions in which for some reason the normal pacemaker is out of action, either in experimental destruction of that region or in cases of vagal slowing, the A-V node may take over the function of pacemaker; in cases of A-V heart-block, likewise, centres low in the bundle below the level of the lesion are responsible for the impulse-production which guides ventricular activity. Less common, but of great interest, are those cases in which two independent rhythms simultaneously compete for control of the heart. The possibility of such a condition was first suggested by Wenekebach,⁶ who proposed the name "pararrhythmia" for the condition. An essential condition of the coexistence of two centres elaborating rhythmic stimuli at different rates is that each should be protected from the other, so that the impulses from the faster working centre do not capture the rhythm by penetrating to the other and destroying the stimuli in process of elaboration there. Such a protective block around each centre (*Schutzblockierung*) was postulated by Kaufmann and Rothberger³ in their description of parasyctole, the particular variety of pararrhythmia to be dealt with in this paper. Given such a condition of protective-block, the simultaneous existence of two stimulus-producing centres in the heart, acting at different rates, and each sending impulses into the ventricular muscle at rhythmic intervals, results in the contractile tissues responding to first one, then the other of the pacemakers: the rhythms can only interfere with one another so far that an impulse from one may arrive to find the muscle

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already in contraction in response to an impulse emanating from the other, or still refractory after such a contraction; in short, the two rhythms will interact to produce what is known as an "interference dissociation." Of this there are many varieties, according to the location of the two pacemakers, their relative rates, the facilities for conduction from chamber to chamber, and the effects of the extrinsic cardiac nerves upon the rhythms of one or both when the centres lie in territory within the sphere of influence of these nerves (e.g., vagal action on centres lying above the ventricular level). "Parasystole" is the term applied to that particular form in which one centre is located in the ventricle, elaborating stimuli at a rate generally slower than the sinus rhythm, which is responsible for the competing second rhythm. The term was introduced in 1917 by Kaufmann and Rothberger, who described cases in which extrasystoles of ventricular origin occurred, scattered here and there, singly and in pairs, throughout long records, and which on analysis displayed the interesting feature that the longer intervals between extrasystoles were always simple multiples of the interval separating a pair of extrasystoles occurring in immediate succession. It was apparent that a second rhythm, elaborating stimuli at the rate whose value was given by these pairs of extrasystoles, could well be responsible for all the extrasystoles in the records. As early as 1912 it had been suggested by Fleming² that some such mechanism might be at work, and although his observations were limited to polygraph tracings, he suggested that in cases showing regularly recurring ventricular extrasystoles "the rhythmical production of stimuli at an abnormally irritable point in the ventricles may produce such rhythmic irregularities."

This conception of parasystole, as developed by Kaufmann and Rothberger,³ Singer and Winterberg,⁵ and by subsequent workers, has been vigorously attacked from many sides. A full account of the theory and of the criticisms levelled against it will be found in the review by Rothberger,⁴ who picturesquely says that the first critics were inclined almost "to throw out the baby along with the bath water." In spite of many objections it appears that the theory affords a valuable means of analysing a certain proportion of cases of extrasystolic arrhythmia. The total number of cases submitted to adequate analysis is not large: Faltitschek and Scherf¹ in 1932 referred to only eleven cases from the literature (including five from their own paper) in which parasystole as a simple interference-dissociation had been established. It has been emphasized that all cases from which full material is available should be published in detail. It is never justifiable to base a diagnosis of parasystole on short records, in which chance coincidence can play so great a rôle; and as in most cases short records alone are available from patients displaying extrasystoles in the clinic, the dearth of adequate analyses is readily understood.

Even when this factor has been given full weight, however, parasystole seems to be in effect a comparative rarity, only a very small percentage of the clinical cases displaying extrasystoles being capable of explanation on this basis. The present case, appearing to fulfill all the criteria justifying the diagnosis, is reported because of the fortunate circumstance that a long continuous electrocardiographic record is available for analysis.

CASE REPORT

J. MacF., male, aged fifty-nine years, a seedsman's manager, was examined as an out-patient at Royal Infirmary, Edinburgh, on Dec. 4, 1933. About one month previously he had been awakened about 5 A.M. by intense pain behind the sternum, which radiated to the left arm and was accompanied by a choking sensation. The intensity of pain overshadowed everything, and the patient could give no clear account of other symptoms beyond stating that "he thought his last day had come." Five very severe attacks of pain were experienced in the space of an hour. The patient was then given amyl nitrite inhalations by his family physician, and went to sleep. There was no recurrence of pain during the two weeks following, for which period he was confined to bed.

Two months prior to this attack, he had had a minor seizure of a similar nature. While playing bowls he felt mild pain, "more a soreness than actual pain," across the chest, accompanied by a choking feeling; this was severe enough to prevent his resuming his game, but next day he played again without recurrence of his symptoms. The patient denied any breathlessness on exertion, but the presence of some dyspnea is indicated by his admission of inability to sing now, though formerly he had been a professional vocalist.

Since his major attack he has had intermittently a hot burning sensation behind the sternum, but no actual pain.

Examination.—Pulse, 64 per minute, irregular in time. Blood pressure 140/90. Radial arterial wall not unduly thickened. Heart: Apex beat in fifth space, $3\frac{1}{2}$ in. from midsternal line. Both sounds were closed and faint. Irregularity was due to audible extrasystoles. X-ray examination showed no cardiac abnormality. Electrocardiographic records described below. Retinae showed early arteriosclerotic changes, no hemorrhages or optic neuritis. Wassermann reaction, negative.

The patient was seen again on Feb. 7, 1934. The burning sensation complained of on previous visit persisted, otherwise he felt well. Good colour, without cyanosis or edema. Pulse, 56 per minute, regular. Blood pressure, 170/110. Other findings as on previous occasion. When seen for the third time on May 1, 1934, the patient still complained of the substernal burning sensation but denied any real pain. Pulse while sitting and at rest was regular, rate 56 per minute. A simple exercise test was carried out, the patient being allowed to walk on the level till pain was experienced. Standing up raised the rate to 64, while walking 40 yards on the level raised it to 67 and extrasystoles began to appear. Blood pressure, 132/88. The exercise was continued till slight pain was produced, when extrasystoles were frequent. Electrocardiographic records were made before and after the exercise test, and are described below.

ELECTROCARDIOGRAMS

Dec. 4, 1933: A routine electrocardiogram (short record) showed a regular sinus rhythm interrupted by ventricular extrasystoles, occurring at times in pairs in immediate succession. The P-waves were upright in all leads, somewhat deformed in

Leads II and III. The P-R interval measured 0.2 second. QRS in all leads measured 0.1 second. In Lead I a very small Q-wave was followed by a slurred R 3 mm. high, and that by an S 3 mm. deep (Fig. 1). T was deeply inverted, S-T not displaced. In Lead II Q was absent; R was slurred and 5 mm. high, and S 8 mm. deep. S-T was not isoelectric. T showed a positive summit 3.5 mm. high followed by a small negative phase. In Lead III Q was absent; R was splintered and of low amplitude (2 mm.), while S was 5 mm. deep and somewhat slurred. S-T elevation to the extent of 1 mm. was present. T was high (5 mm.) and positive. The appearances suggested a coronary infarct (anterior type) of some weeks' duration. An interesting feature of the record is that where two extrasystoles appeared in immediate succession, the final deflections of the first were deformed by a superimposed P-wave: the succeeding F-wave preceded the second extrasystole by a short interval (about 0.1 second), and by measurement of P-P intervals on the

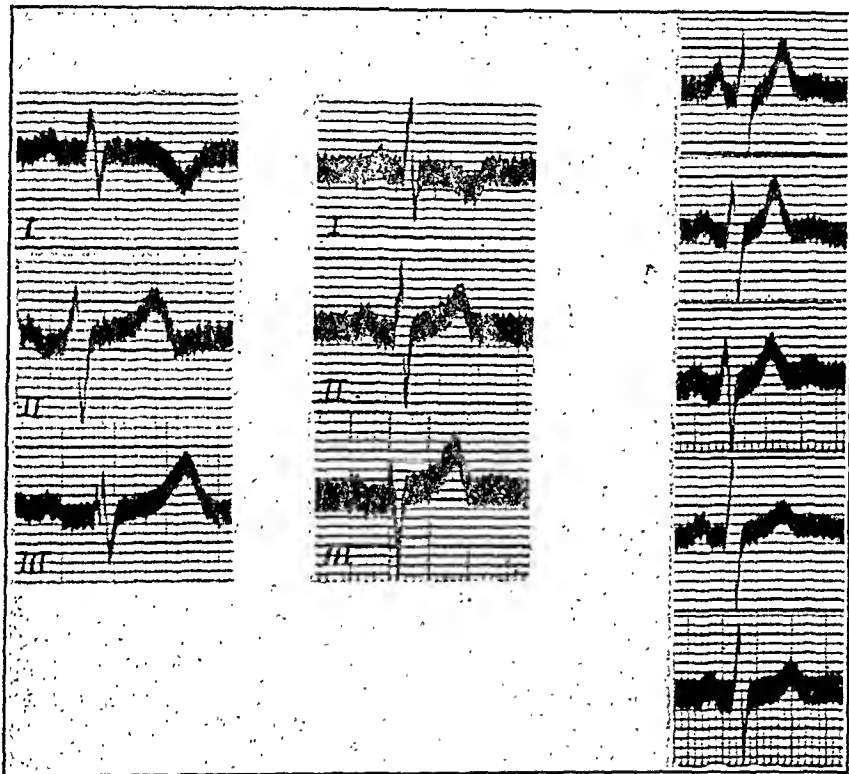


Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1.—Electrocardiogram, Dec. 4, 1933. Leads I, II, and III. In this and succeeding records time-marker is in fifths and twenty-fifths of a second, and standardisation is 1 cm. per millivolt.

Fig. 2.—Electrocardiogram, May 1, 1934, Leads I, II, and III.

Fig. 3.—Electrocardiograms, May 1, 1934, Lead II. The first record was taken immediately on cessation of exercise, the others at short intervals during the succeeding four minutes. Mild anginal pain was present when record 1 was taken.

curve it could be determined that rhythmic sinus impulses were responsible for all auricular deflections and that retrograde conduction was not responsible for those seen deforming the terminal deflections of the extrasystolic complexes.

Dec. 11, 1933: A short record in the three leads displayed similar features to that of a week before, although only single extrasystoles were then recorded. A film record taken on this date, however, displayed numerous extrasystoles, the analysis of which forms the basis of this communication (see below).

Feb. 6, 1934: Normal sinus rhythm, without extrasystoles. P-R interval still 0.2 second. Ventricular complexes of larger amplitude than in previous records, but of same general form. T in Lead I was more deeply inverted (−6 mm.), and

S-T in that lead depressed 1 mm. T-waves in Leads II and III were sharply positive. Such changes as had occurred from previous records were consistent with the original diagnosis of coronary infarct.

May 1, 1934: An electrocardiogram taken at rest showed features (Fig. 2) practically identical with those described Feb. 6, 1934, T in Lead I remaining sharply inverted, though smaller, T₂ and T₃ positive. Extrasystoles were absent. Following the exercise test referred to in the case report, serial electrocardiograms were made by Lead II over the space of several minutes. The rate rose from its resting value of 54 to 100 per minute and fell gradually to its original level on resting. The return to the slower rate was attended by the appearance of ventricular extrasystoles, which were similar in form to those recorded on previous occasions in this patient. Unfortunately, only short records, unsuitable for analysis, were secured. A striking change in the T-waves was noted in these records. The T-wave in Lead II before exercise measured +3 mm.; immediately after cessation of the exercise it measured +5 mm., and was markedly peaked in outline. A gradual return to the previous amplitude and form was observed in successive records (Fig. 3).

ANALYSIS OF FILM RECORD

Upward of 170 ventricular systoles were included in the film record obtained from the case, a portion of which is reproduced in Fig. 4, together with a diagrammatic representation of the probable mechanism involved. It will be seen from the electrocardiogram that a regular sinus rhythm is present, interrupted by ventricular extrasystoles scattered throughout the record, occurring singly and in pairs. When the intervals separating successive extrasystoles on the record are examined, they are found to be simple multiples of an interval approximating that which separates neighbouring extrasystoles occurring in immediate succession. For example, the interval between complexes 112 and 113 measures 138×0.01 second. (All measurements are in 0.01 second.) The interval between complexes 113 and 117, the next succeeding extrasystole visible on the curve, measures 406, or three times 135.3. Similarly, the interval between complexes 117 and 122 measures 544, or four times 136; and the interval 108 to 112 measures 409, or three times 136.3. It is at once apparent that the extrasystoles do not occur haphazard, irregularly scattered through the record, but obey a rhythm whose fundamental period is about 135 to 138 hundredths of a second. If we draw in above the curve a scheme representing the sinus rhythm, and insert upon it arrows to represent a rhythm of the value found above, we see the mechanism clearly at once. When a stimulus of the second rhythm (the para-rhythm) falls during diastole, the ventricles respond by an extrasystolic contraction. When such a stimulus falls, however, during the systole of the ventricles, it is ineffective because of the refractory state of the ventricular muscle. All stimuli falling within a short period of the end of the T-wave are ineffective for a similar reason, the ventricle being relatively refractory for some little time after T is written (see below, under "Refractory Period"). At sev-

eral points on the record, para-stimuli fall at a time when a supra-ventricular stimulus is due; for example, the next para-stimulus after that which produced complex 108 falls approximately 0.3×0.01 second after the normal stimulus arriving from the A-V bundle is due. When we look at the electrocardiogram, we find that complex 109 is in effect intermediate in form between the extrasystolic form (108) and the

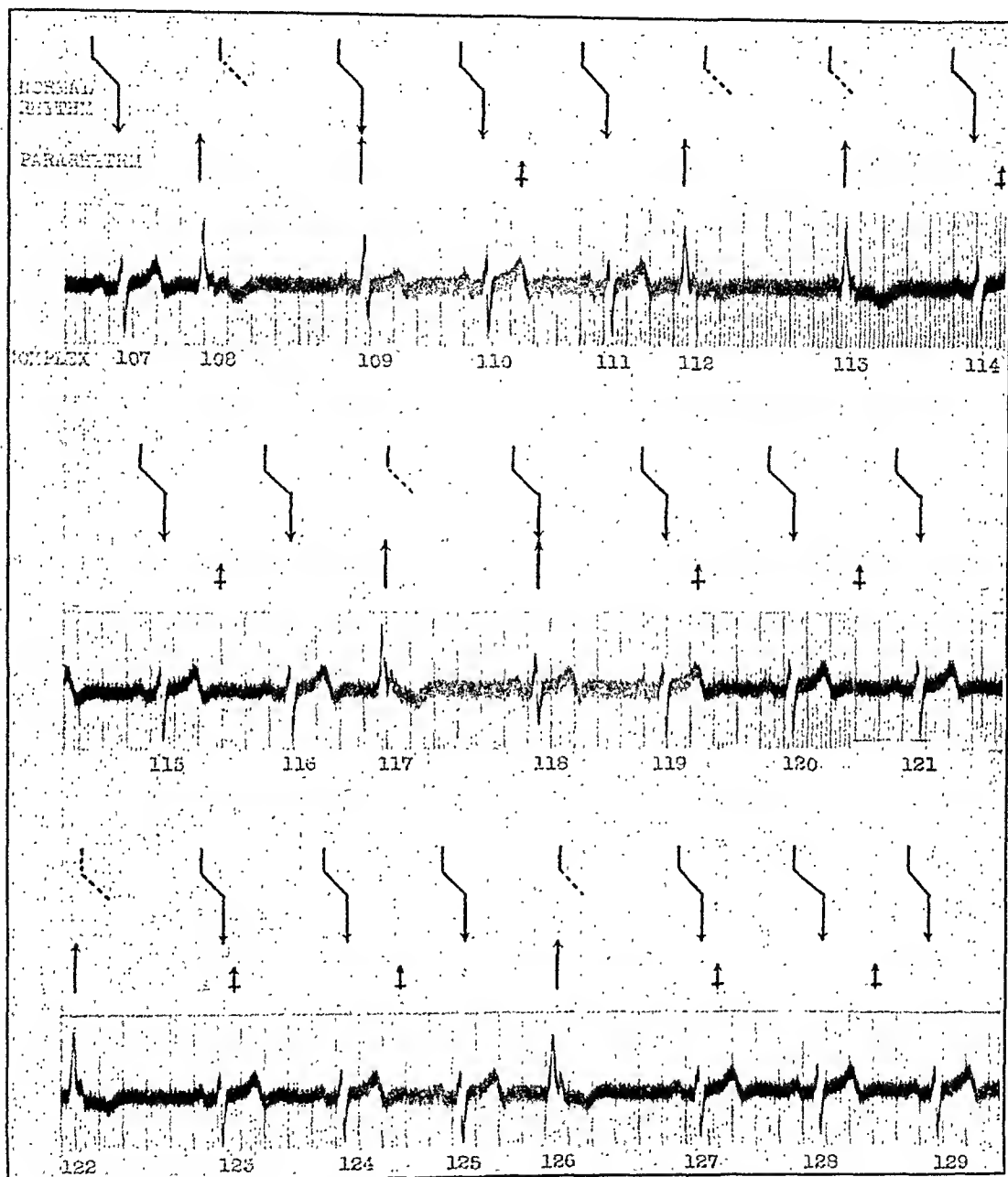


Fig. 4.—Electrocardiogram, Lead II; complexes 107 to 129 from the film record made on Dec. 11, 1933. The scheme above the record represents the interplay of the two rhythms. (See text and Table I.)

normal form (110); it appears that the two stimuli emanating from different points have met in the wall of the ventricles and have combined to produce a "mixed complex," analogous to those produced experimentally by Wilson and Herrmann.⁷ These authors found that when the branch of the His bundle supplying one of the ventricles in

the dog had been cut, rhythmic stimulation of the ventricle supplied by that branch at a rate faster or slower than the sinus rate led to the appearance of "mixed complexes," transitional between those characteristic of stimulation of that ventricle and the opposite type produced by sinus beats with bundle-branch block affecting the conduction tissue to the side in question. In their case a well-timed stimulus, so released that the impulse from the auricle reached one ventricle via the intact branch of the bundle simultaneously with the activation of the opposite ventricle by the electrical stimulus, produced by summation of effects a normal complex. So in the present case, activation from the para-centre occurring simultaneously with activation from the normal supraventricular centre produces a type of complex intermediate between the two extreme forms characteristic of activation from either centre alone. Complex 109 is not alone in this configuration in the record reproduced: complex 118 is also intermediate in form between the normal and the extrasystolic types, and from the scheme we find that a para-stimulus falls 4.0×0.01 second after the normal beat is due. In the case of complex 113 we see immediately before it a rhythmic P-wave; the P-R interval is much shorter than normal (0.1 second), and it is apparent that the para-stimulus has already produced its full effect before the rhythmic stimulus arrives from the A-V bundle. The rhythmic stimulus, finding the ventricles already in contraction, is rendered ineffective in the same fashion that many of the para-stimuli are frustrated. We have in the record reproduced, therefore, evidence of simultaneous presence in full activity of two independent rhythms whose basic intervals bear no simple relation one to another (sinus rhythm about 56 per minute, para-rhythm about 44 per minute), and whose impulses interfere on occasion in the course of their spread through the ventricular muscle to produce complexes of mixed form. Before the diagnosis of parasystole with simple interference can be made absolute, analysis of a longer curve is necessary, and we will now proceed to consider the film record in its entirety.

Table I is modelled on those published by Singer and Winterberg,⁵ and some explanation of its arrangement is necessary. The table is divided into sections by horizontal lines, each section containing from one to seven rows of figures. Starting from the first extrasystole on the record, the consecutive ventricular complexes have been numbered serially, and these numbers appear in the first column of the table. In the second column is the time interval between each complex and that preceding, irrespective of whether the complex be normal or extrasystolic. (All intervals are in hundredths of a second; these have been measured approximately from the curve, on which time markings were in $\frac{1}{25}$ and $\frac{1}{5}$ seconds. Comparator readings were not used, being considered unnecessary for the present purpose.) The

last complex in each section is an extrasystole: where only one complex occurs between a pair of lines, it is the second of a pair of extrasystoles occurring in immediate succession (e.g., complex 2, complex 113). The figures in the third column are the measured intervals from any normal complex to the last preceding extrasystole; e.g., the figure 220 opposite complex 115 indicates that complex 115 occurred 220×0.01 second after the last preceding extrasystole, complex 113. Similarly, in the fourth column are found corresponding values for the extrasystolic complexes: the extrasystole 117 occurs 406×0.01 second after the preceding extrasystole 113. The italicized figures in the fifth column indicate the interval separating any extrasystole from the last preceding normal beat, the "manifest coupling." In the sixth column are found the average values for the sinus-rhythm interval for each section, while in the last column are the average values for the para-rhythm intervals, as calculated by dividing the figures in column 4, by the number of para-intervals included in the section. For example, the section 114 to 117, which is figured in Fig. 4, contains three para-cycles, whose average value is thus 135.3 ($3 \times 135.3 = 406$). There remain to be explained the nonitalicized figures in column 5. These are the "latent couplings" and are calculated as follows: Having found the average para-interval for each section, we calculate what relation each para-stimulus must bear to the stimuli of the normal supraventricular rhythm. Complex 114, for example, falls 114×0.01 second after the extrasystole 113; a para-stimulus is due 135.3×0.01 second after that extrasystole, that is, 21.3×0.01 second after the normal beat 114. We may enter that figure 21.3 in column 5 as a "latent coupling," indicating where an extrasystole would have occurred had the ventricle not been refractory. Similarly, another para-stimulus was due at 2×135.3 after complex 113, that is 270.6 after that extrasystole. The normal beat 115, however, fell at 220 after complex 113, so again the para-stimulus was frustrated, falling 50.6 hundredths of a second after the ventricle had passed into contraction. We enter 50.6 as the latent coupling for complex 115—and so on. Certain of the latent couplings are very short, between 0.3 and 0.04 or 0.05 second; a few are entered as negative quantities of small magnitude. These indicate that a para-stimulus and a normal stimulus fell very nearly together; according to our theory, such should result in "mixed beats." The asterisks opposite certain of the figures in column 5 indicate such mixed complexes as are actually visible on the record, and it will be noted how closely observation accords with theory in this respect. (See also below, "Combination Complexes.")

Consideration of the table shows that a para-rhythm can be postulated which will account for the observed phenomena throughout. The occurrence of the mixed or combination complexes is strong corroborative evidence of the simultaneous presence of two rhythms.

TABLE I

COMPLEX NUMBER	CONSEC- UTIVE VENT. CYCLES	NORMAL BEATS: OC- CURRENCE	EXTRA- SYSTOLES: OC- CURRENCE	COUPLINGS	AVERAGE CYCLE (NORMAL RHYTHM)	AVERAGE CYCLE (PARA- RHYTHM)
1	66		66	66		
2	130		130			130
3	114	114		18.6		
4	102	216		49.2		
5	98	314			103.4	132.6
6	84		398	84		
7	119	119		12		
8	92	211		51		
9	96	307			101	131
10	86		393	86		
11	112	112		29.2		
12	100	212		70.4		
13	100	312				
14	100	412		11.6	102.5	141.2
15	102	514		51		
16	102	616				
17	90		706	91		
18	114	114		34		
19	100	214			98	148
20	82		296	82		
21	112	112		35		
22	98	210			96	147
23	84		294	84		
24	106	106		37		
25	100	206			100	143
26	80		286	80		
27	120	120		22		
28	102	222			101.3	142
29	62		284	62		
30	140	140		-3*		
31	102	242		44.6		
32	102	346			102	143.3
33	84		430	84		
34	120	120		23		
35	106	226			105.3	143
36	60		286	60		
37	150	150		-6*		
38	108	258		30		
39	108	366			105.5	144
40	66		432	66		
41	140	140				140
42	108	108		34		
43	104	212			103	142
44	72		284	72		
45	128	128		13.3		
46	106	234		48.6		
47	106	340			106	141.3
48	84		424	84		
49	128	128		13.6		
50	108	236		49.2		
51	110	346			106.8	141.6
52	79		425	79		
53	130	130		10.6		
54	104	234		47.2		
55	102	336			102	140.6
56	86		422	86		

TABLE I—CONT'D

COMPLEX NUMBER	CONSECU- TIVE VENT. CYCLES	NORMAL BEATS: OC- CURRENCE	EXTRA- SYSTOLES: OC- CURRENCE	COUPLINGS	AVERAGE CYCLE (NORMAL RHYTHM)	AVERAGE CYCLE (PARA- RHYTHM)
57	116	116		26		
58	100	216			100	142
59	68		284	68		
60	132	132		6.6		
61	100	232		45.2	100	138.6
62	98	330				
63	86		416	86		
64	116	116		20.6		
65	100	216		57.2	105	136.6
66	106	322				
67	88		410	88		
68	126	126		7.6		
69	103	229		38.6	104.8	133.6
70	104	333				
71	68		401	68		
72	134	134		2.6		
73	100	234		39.2	100.5	136.6
74	102	336				
75	74		410	74		
76	126	126		12		
77	104	230		46	105	138
78	106	336				
79	78		414	78		
80	132	132		5.8		
81	112	244		31.5	113.8	137.8
82	112	356		57.3		
83	110	466				
84	85		551	85		
85	136	136		2		
86	110	246		30	105	138
87	106	352				
88	62		414	62		
89	142	142				142
90	110	110		32.5		
91	102	212			105.5	142.5
92	73		285	73		
93	136	136		5.3		
94	104	240		42.6	105	141.3
95	106	346				
96	78		424	78		
97	132	132		10		
98	106	238		46	107	142
99	110	348				
100	78		426	78		
101	134	134		8*		
102	112	246		38	107	142
103	108	354				
104	72		426	72		
105	136	136		2.6*		
106	106	242		35.2	104	138.6
107	106	348				
108	68		416	68		
109	136	136		0.3*		
110	104	240		32.6	102.8	136.3
111	104	354				
112	65		409	65		

TABLE I—CONT'D

COMPLEX NUMBER	CONSECUTIVE VENT. CYCLES	NORMAL BEATS: OC-CURRENCE	EXTRA-SYSTOLES: OC-CURRENCE	COUPLINGS	AVERAGE CYCLE (NORMAL RHYTHM)	AVERAGE CYCLE (PARA-RHYTHM)
113	138		138			138
114	114	114		21.3	107.6	135.3
115	106	220		50.6		
116	108	228				
117	78		406	78		
118	132	132		4*	107.2	136
119	110	242		30		
120	108	350		58		
121	108	458				
122	86		544	86		
123	124	124		12	102	136
124	102	226		46		
125	104	330				
126	78		408	78		
127	126	126		11.3	102	137.3
128	102	228		46.6		
129	102	330				
130	82		412	82		
131	122	122		15.3	105	137.3
132	104	226		48.6		
133	102	228				
134	84		412	84		
135	130	130		18	107.1	148
136	106	236		60		
137	104	340				
138	108	448		—1*		
139	108	556		36		
140	110	666				
141	74		740	74		
142	139		139			139
143	105			22.3	101.3	137.3
144	102	207				
145	68		275	68		
146	130	130		5.3*	98	135.5
147	96	226		44.6		
148	98	324				
149	82		406	82		
150	116	116		20	104.5	136
151	98	214		56		
152	106	320				
153	88		408	88		
154	126	126		28	108.3	154
155	108	234		74		
156	108	342				
157	106	448		14		
158	105	553				
159	63		616	63		
160	142	142		—4*	101.8	138
161	102	244		30		
162	100	344				
163	70		414	70		
164	123	123		7.3	101	130.3
165	98	221		39.6		
166	96	317				
167	74		391	74		

*Mixed complexes actually visible on the record. (See text.)

The para-intervals in Table I show variation between extreme values of 130 and 154: the majority of transitions occur gradually, and there are but three instances in the whole record where sudden variations amounting to 4×0.01 second or more occur. [These instances are (a) between complexes 10 and 18, where the intervals lengthen from 131 to 148×0.01 second; (b) between complexes 134 and 142, where the para-interval temporarily lengthens from 137.3 to 148, returning again to 139×0.01 second; and (c) between complexes 153 and 160, where the para-intervals again temporarily lengthen from 136 to 154 hundredths of a second.] The first and third of these sudden variations are the subject of discussion below, under the head "Latent Couplings"; the second is interesting in that a mixed complex occurs in the middle of the section with the slower parasythm, and that in a position predictable from the table (complex 138), so that the calculated para-intervals are in this instance substantiated by direct observation.

Refractory Periods.—In their original papers on the subject, Kaufmann and Rothberger took as a measure of the refractory period the duration of QRST—i.e., the absolute refractory period. It was later suggested by Singer and Winterberg that this might not represent the actual effective refractory period; a state of partial refractoriness supervenes at the end of the absolute refractory phase, and it is possible that the ventricle may persist in a refractory state for some little time after the end of T, at least so far as stimuli of the strength of those emanating from our hypothetical "para-centre" are concerned. As we have no measure of the strength of these stimuli and no means of testing the ventricular refractory period directly, we must have recourse to indirect methods. It was suggested by Singer and Winterberg that if one found a "latent coupling" which consistently failed to produce an extrasystole, and close to it in magnitude a "manifest coupling" which consistently was followed by an extrasystole, then the refractory period for stimuli of the particular strength here concerned must lie between these two values. On examination of Table I we note that the "latent couplings" of 57.2 (complex 65) and 57.3 (complex 82), 58 (120) and 60 (136), are not followed by responses; while the "manifest couplings" 60 (complex 36) and 62 (complexes 29 and 88) are followed by extrasystoles. The relative refractory period, therefore, by this method, lies between 57.3 and 62 hundredths of a second, probably close to 60×0.01 second.

Scrutinising the column of "couplings" with this value for the refractory period as standard, we find that with two exceptions all couplings above the value of the refractory period are "manifest," i.e., whenever a para-stimulus falls late enough in diastole to be outside the relative refractory period, an extrasystole results. The two

exceptions are complexes 12 and 155, with "latent" couplings of 70.4 and 74, respectively. The explanation of this inconsistency will be discussed below. (See "Exit-block.")

"*Exit-Block.*"—Of the various auxiliary theories which have been introduced as part of the theoretical superstructure erected upon the simple conception of parasystole as we have so far defined it, that of *Austrittsblock* has perhaps given rise to most controversy. By the term, which we may translate as "exit-block," the idea is conveyed that certain of the impulses arising in the para-centre are unable to pass out freely into the neighbouring muscle, and that a condition of block exists between para-centre and muscle comparable to that produced between auricle and ventricle by lesions of the auriculoventricular bundle. The necessity for such an hypothesis arises in some cases of apparent parasystolic rhythm in which frequent para-stimuli fall during ventricular diastole outwith the relative refractory period, without ventricular extrasystoles appearing in the record. A close parallel with A-V block is provided by these instances (Singer and Winterberg⁵) where the para-rhythm as measured directly between a pair of extrasystoles occurring in immediate succession is slightly longer than that calculated from subdivision of long intra-extrasystolic intervals, as though the second emerging impulse had been delayed in similar fashion to prolongation of the P-R interval in first stage of A-V heart-block. It finds its main application, perhaps, in the explanation of certain cases of paroxysmal tachycardia, in which the records between attacks display extrasystoles of the same form and presumably the same origin as the complexes constituting the paroxysms, and the intervals between the extrasystoles are simple multiples of that separating the complexes during a paroxysm. An obvious explanation for such a condition is to postulate a rhythmic para-centre, whose activity persists at the same high rate irrespective of whether a paroxysm is or is not present: during a paroxysm each stimulus elaborated in the centre reaches the ventricular muscle and each produces a response, the high inherent rate of the ectopic centre being sufficient to ensure its capturing the rhythm. Between paroxysms, on the other hand, the presence of some degree of "exit-block," sufficient to prevent most of the stimuli from reaching the muscle while allowing an occasional impulse to escape, would account for the observed regular sinus rhythm broken by occasional extrasystoles of similar form to those constituting the paroxysm, whose spacing indicates that they belong to the same fundamental rhythm as the beats in a paroxysm. Cases have been described where "exit-block" has to be postulated in the analysis of a parasystole case such as we here describe, in the absence of paroxysmal tachycardia, and this is especially so when the absolute refractory period, as calculated from the duration of QRST, is taken as a measure of the lowest permissible

coupling, instead of the relative refractory period calculated by the method of Singer and Winterberg detailed above. Cases in which the relative refractory period is taken into account, and which still necessitate exit-block as an auxiliary, are generally those where the para-rhythm is faster than the sinus rhythm. (Faltitschek and Scherf.¹)

In the analysis of the case under consideration, there are but two instances where a "para-stimulus" falls in diastole outwith the refractory period of the ventricles, and no response is apparent in the record. In Table I these long couplings without manifest responses occur in the cycles 12 and 155. The nonappearance of extrasystoles in these cycles could be explained on any one of four grounds: (1) a rhythmic para-stimulus was not elaborated at that time; (2) the ventricle was still refractory when the stimulus arrived; (3) the stimulus was of lower intensity than usual; or (4) "exit-block" was present and the elaborated stimulus did not reach the ventricle. The second and third possibilities may be considered together, since we are dealing with the relative refractory period, whose duration depends closely on the strength of stimulus concerned. It might be that a stimulus of lowered intensity had been elaborated, to which the ventricle remained refractory, a possibility we have no means of proving or disproving; that the refractory period to a stimulus of similar intensity to the other para-stimuli should in this particular instance be prolonged seems highly improbable. The "exit-block" hypothesis would obviously afford a simple explanation, but we are faced with the problem why in these particular cycles the emerging para-stimuli should have been obstructed, when in the other fifty instances in the record in which a para-stimulus fell during the non-refractory phase, no such exit-block was apparent. The first possibility, that a para-stimulus was not elaborated at that precise moment, demands further consideration. It will be noted from a scrutiny of Table I that in both cases when such a long "latent coupling" occurred there was a coincident and abrupt transition in the rhythm of the para-centre from a faster to a slower rate. For example, over the cycles 7 to 10 the para-rhythm interval averaged 131×0.01 second; over the cycles 3 to 6, 132.6 hundredths second; and for the directly measurable cycle 1 to 2, 130 hundredths second. The long latent coupling occurred during the section including cycles 11 to 17, where the average para-rhythm cycle averaged 141.2×0.01 second. The average para-rhythm cycle for section 18 to 20 was 148×0.01 second; for cycles 21 to 23, 147×0.01 second, and for cycles 24 to 26, 143×0.01 second. A sudden transition from a shorter para-rhythm interval to one longer by 17×0.01 second therefore occurred during the section including cycles 11 to 17. Similarly, in the other instance of long latent coupling, the directly measured para-interval for cycle 142 measured 139×0.01 second; for cycles 143 to 145 it averaged 137.3×0.01

second; for cycles 146 to 149, 135.5×0.01 second; for cycles 150 to 153, 136×0.01 second. For the section including the long latent coupling (154 to 159) the para-interval averaged 154×0.01 second; for the succeeding cycle 159 to 160 it was measured as 138×0.01 second; and for cycles 161 to 163 it averaged 138×0.01 second. Again the section including the abnormally long latent coupling was one of transition from short to longer para-interval. In the computation of the latent couplings in the table it has been assumed that the para-rhythm over the whole of a section remained constant at its average value for that section, and that when transitions occurred they did so suddenly in the cycles demarcating sections—both assumptions that are in fact highly improbable. If we assume, as is much more likely, that transitions occurred gradually over the space of several para-cycles, then recalculation of the latent couplings for these sections is necessary, the effect being to shift the earlier couplings somewhat forward and thus to shorten those which appear abnormally long in the original table.

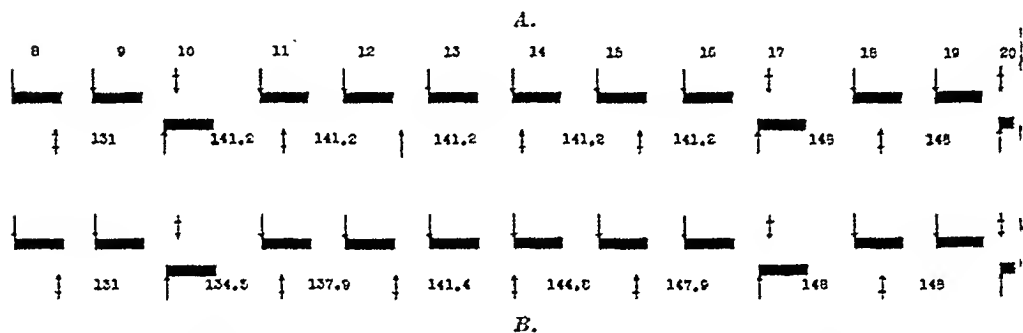


Fig. 5.—Diagrams drawn to scale, representing alternative relationships of the two rhythms between cycles 8 to 20 of the film record. In each diagram the upper row of downwardly directed arrows indicates the successive ventricular responses to supraventricular impulses. The lower row (upwardly directed) indicates the para-rhythm stimuli. Black rectangles indicate the times during which the ventricles are refractory, and crossed arrows of either series indicate stimuli ineffective through falling during these refractory periods.

In Fig. 5A the para-interval is supposed to increase abruptly from 131 to 141.2×0.01 sec., remaining at that value for five cycles before increasing further to 148. The fourth para-stimulus is seen to fall outwith the ventricular refractory period, without producing a response.

In Fig. 5B the para-interval is drawn as increasing by equal increments from 131 to 148×0.01 sec. The anomalous para-stimulus is now seen to fall within a period of ventricular refractoriness.

In Fig. 5 the effect of such a modification of the calculated para-rhythm intervals upon the latent couplings in cycles 8 to 10 is shown diagrammatically. When the transition from fast to slower rhythm is assumed to occur abruptly, the time relations of the para-stimuli to the ventricular refractory periods are as shown in Fig. 5A; an obvious discrepancy is notable in cycle 12 to 13, in which a para-stimulus falls outwith the refractory period without provoking a response. On the other hand, when a gradual but regular increase in the successive para-intervals is assumed to occur, each interval from that succeeding complex 10 being longer than its predecessor by 3.45×0.01 second,

till the value 147.9 is reached in the cycle preceding complex 17, the long latent coupling in question is materially shortened (Fig. 5B).

In the other series (complexes 154 to 159), such a modification of the calculated para-rhythm does not entirely obviate the difficulty. The para-rhythm here has the following values: 2×137.5 ; 3×134.5 ; 3×136 ; 4×154 ; 3×138 . The long para-interval is in this case not maintained after the group 154 to 159, but falls at once to the old value of around $137-138 \times 0.01$ second. Assuming that the transition to a longer interval occurred gradually and that the return was also gradual, all in the space of four para-cycles, one must assume a very high value (circa 175×0.01 second) for the longest cycle, if the average of 154×0.01 second for the whole group is to be maintained. This seems unwarranted, unless some other mechanism can be shown (or postulated) to account for the long cycle. A feasible explanation is the possibility of momentary failure of the protective block (*Durch-*

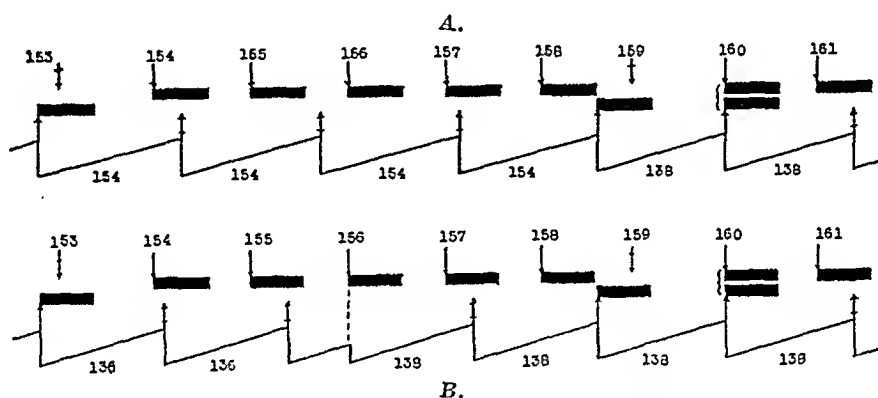


Fig. 6.—Diagrams drawn to scale as in Fig. 5, with the addition of a scheme indicating the building-up of the impulses in the ectopic centre. Cycles 153 to 161 are represented. (See Table I.)

In Fig. 6A, where the para-rhythm is shown as 154×0.01 sec. for four cycles, then returning to 138, the third para-stimulus falling between complexes 155 and 156 provokes no response.

In Fig. 6B the anomaly is seen to be obviated if the supraventricular impulse 156 penetrates to the para-centre and destroys the impulse in process of elaboration. The para-interval remains practically constant at $136-138 \times 0.01$ sec.

bruch der Schutzblockierung) which is represented diagrammatically in Fig. 6. The upper of the two diagrams in that figure shows the mechanism if the para-rhythm be assumed to increase from 136 to 154×0.01 second for five cycles: cycle 155-156 shows the para-stimulus falling late in diastole without ventricular response, which demands explanation. In the lower diagram is shown the alternative mechanism. The para-centre is shown elaborating impulses at intervals of 136×0.01 second. The sequential complex 156 is assumed to penetrate the exit-block and destroy the stimulus in process of elaboration so that the para-centre must begin again to elaborate a stimulus from the beginning. From the diagram it is clear that if stimulus production goes on at practically the old rate (138×0.01 second instead of

136), the appearance of the subsequent extrasystoles 159 and 160 can be accounted for without difficulty.

It is not claimed that these explanations represent beyond all doubt the mechanism involved; they are put forward for consideration only, as alternatives to the assumption of *Austrittsblock* in the explanation of the long latent couplings. Their acceptance or rejection does not materially affect the conclusion that the case is one of parasystole with interference, since in the long record analysed these intervals alone are paradoxical; and the evidence of a second "interfering" para-rhythm is conclusive (divisibility of intervals and presence of all grades of transition complexes). One must emphasise, as has been done by Rothberger, that it is not to be expected that a record from a clinical case will conform with mathematical accuracy to our analysis. Even under experimental conditions, where the "para-centre" is replaced in the dog heart by rhythmic stimuli from an electric contrivance, conformity to law is not absolute. The variations possible under clinical conditions are manifold and incalculable, and in analysis one is faced with that element of uncertainty inherent in biological work as contrasted with that employing physicochemical systems of less complexity under controllable conditions.

Combination Beats.—In Fig. 7 is reproduced a series of complexes illustrating the various forms of combination beats encountered in the record. The first complex of each pair is always a frank extrasystole; the second is a "mixed beat" showing combination of the two impulses in varying time relations. In Fig. 7A the second complex is of pure extrasystolic form: a P-wave is visible preceding the ventricular complex by 0.1 second, and it is apparent that the para-stimulus has forestalled the supraventricular stimulus by the difference between this interval and the usual P-R found before normal complexes elsewhere in the record, that is by 0.1 second. The last pair of complexes figured (Fig. 7H) depicts an extrasystole followed by a normal supraventricular complex, the latent coupling in this instance being 18×0.01 second. Between these two extremes all gradations are met with in the record. The second complex of Fig. 7B closely approximates to the extrasystolic form; here again a P-wave is visible, but P-R in this instance is 0.16 second: the para-stimulus precedes the supraventricular by only 0.04 second, and some interference has taken place. In Fig. 7C the P-R of the second complex is normal (0.2 sec.), and the ventricular complex shows further modification, particularly in the depth of S and in the sign of the T-wave. Actually from Table I it will be noted that the latent coupling for this complex was calculated at -4×0.01 second. The second complexes in D, E, F and G of the same figure show progressive modification of the ventricular com-

plexes in the direction of the normal supraventricular type: the latent couplings as calculated for these complexes are respectively -3 ; 4 ; 2.6 ; and 5.3×0.01 second. There is thus close correspondence between the form of the mixed complex and the relation of para- and supraventricular stimuli to one another.

Couplings.—The manifest couplings in the table have been examined with a view to determining whether these showed any tendency for the extrasystoles to occur at a particular point in diastole, or whether

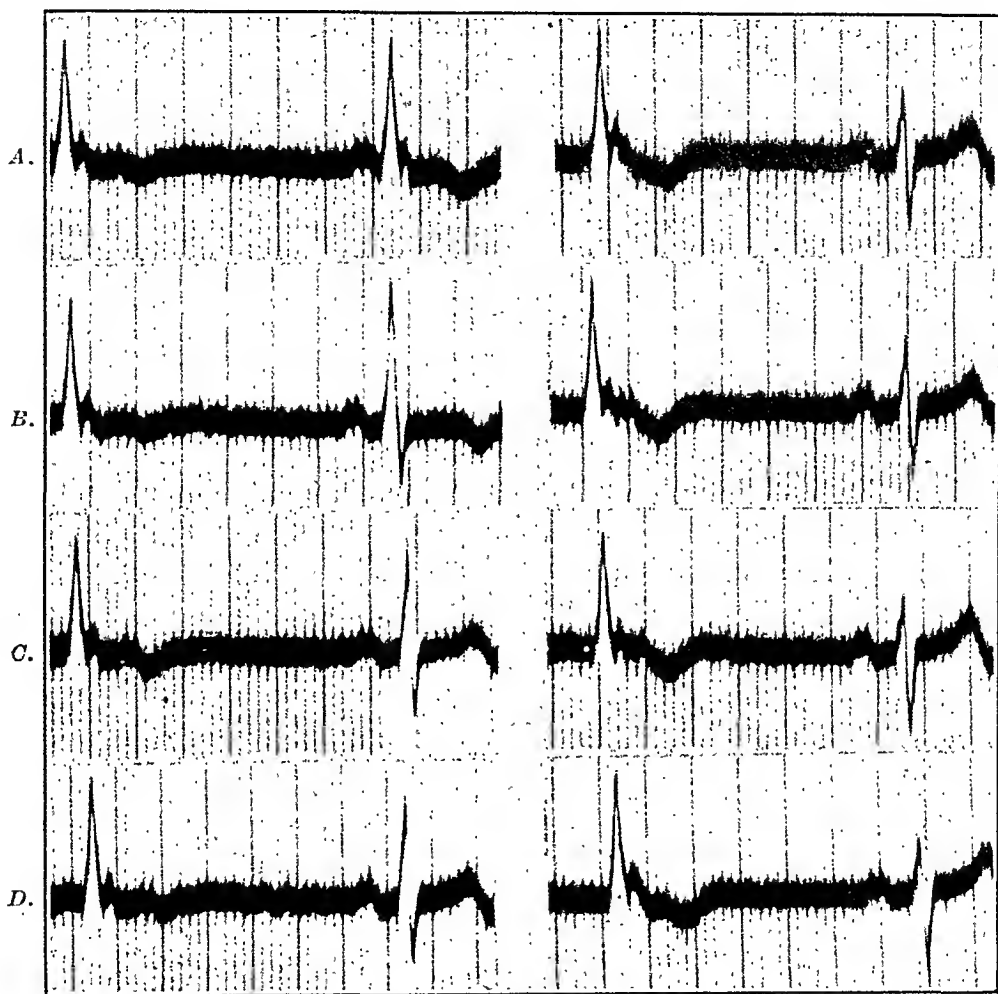


Fig. 7.—Electrocardiograms, Lead II, showing various forms of "combination complexes" from pure extrasystole (7A) to pure supraventricular (7H). The bracketed figures below indicate the time relation of R of the second complex of each pair to "R" of the expected sequential beat, calculated as in Table I. All values in 0.01 second.

7A Complexes 112-113 (-10)
 7B Complexes 1 $\frac{1}{2}$ -1 $\frac{1}{2}$ (-4)
 7C Complexes 159-160 (-4)
 7D Complexes 29-30 (-3)

7E Complexes 117-118 ($+4$)
 7F Complexes 104-105 ($+2.6$)
 7G Complexes 145-146 ($+5.3$)
 7H Complexes 134-135 ($+18$)

they occurred scattered evenly throughout that interval. In Fig. 8 the results of the examination are depicted schematically, abscissae representing the various lengths of coupling, and ordinates the number of times each coupling occurred. It will be seen that all couplings lie in the period from 60 to 91×0.01 second after the preceding systole. The lower limit of this period we have seen to coincide with the

end of the relative refractory period: the upper limit is not clearly defined. Combination complexes have been omitted from this analysis: had they been included we would have had a fresh series of ordinates, 10 in all, distributed in the region of 99 to 114. There would still be a considerable gap between 91 and 99 without manifest couplings. The distribution of the couplings between 60 and 91 is seen to be fairly even, with some increased frequency in the region of 77 to 85.

SUBSEQUENT EXAMINATION

The patient again reported for examination on March 1, 1935, fifteen months after his first visit. He was in fair health but still complained of preeordial discomfort on exertion. Physical examination revealed no significant alteration in the signs since examination a year before.

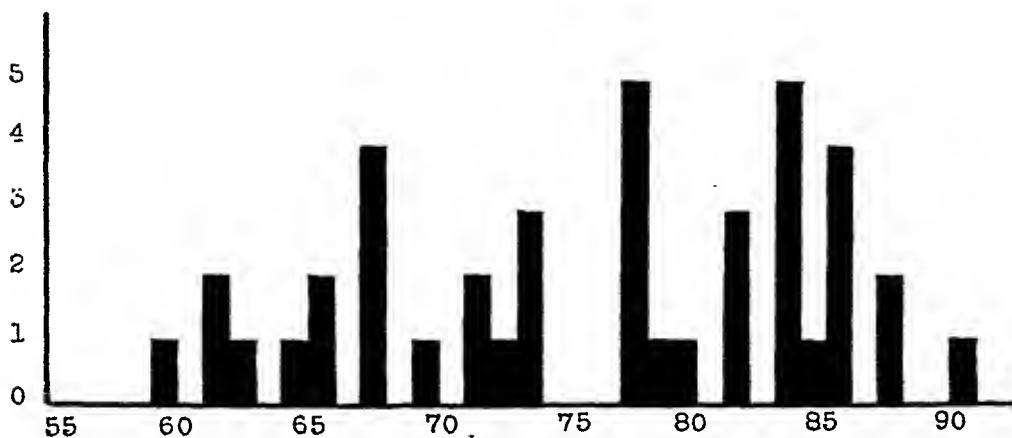


Fig. 8.—Graph showing distribution of couplings.
 Abscissae: Coupling in hundredths of a second.
 Ordinates: Number of instances each value occurred.

Electrocardiogram was made by Lead II after exercise. This film record, comprising 217 ventricular complexes, displayed normal rhythm with an initial rate of 112 per minute. After 68 seconds one ventricular extrasystole occurred, the rate having fallen to 66 per minute. One minute later the rate remaining approximately constant, ventricular extrasystoles were frequent. The T-waves showed similar changes to those described above (see record of May 1, 1934); the amplitude of T immediately after exercise was 7 mm., thirteen seconds later it was 8 mm., falling gradually to 5 mm. at 120 seconds.

The extrasystoles were of strikingly similar form and distribution to those in the record already analysed. Their spacing suggested the possibility of a "para-rhythm," and the record was examined critically to determine whether this was so. Measurements were made from the curve embracing all but the first isolated extrasystole and are given in Table II, which has been compiled in similar fashion to Table I.

It will be seen that a para-rhythm of slow rate can be demonstrated in this curve. The para-rhythm shows no sudden variations, all changes being gradual. The cycles shorten from an initial value of 149×0.01 second, to a minimum of 135×0.01 second, gradually increase again to 144×0.01 , and finally shorten to 139×0.01 second at the end of the record. One mixed or combination complex occurs in the record (complex 17 of Table II), and this is reproduced in Fig. 9. It occurs at a point where by calculation normal and ectopic beats fall precisely together, and corresponds in form to the combination complex in Fig. 7E.

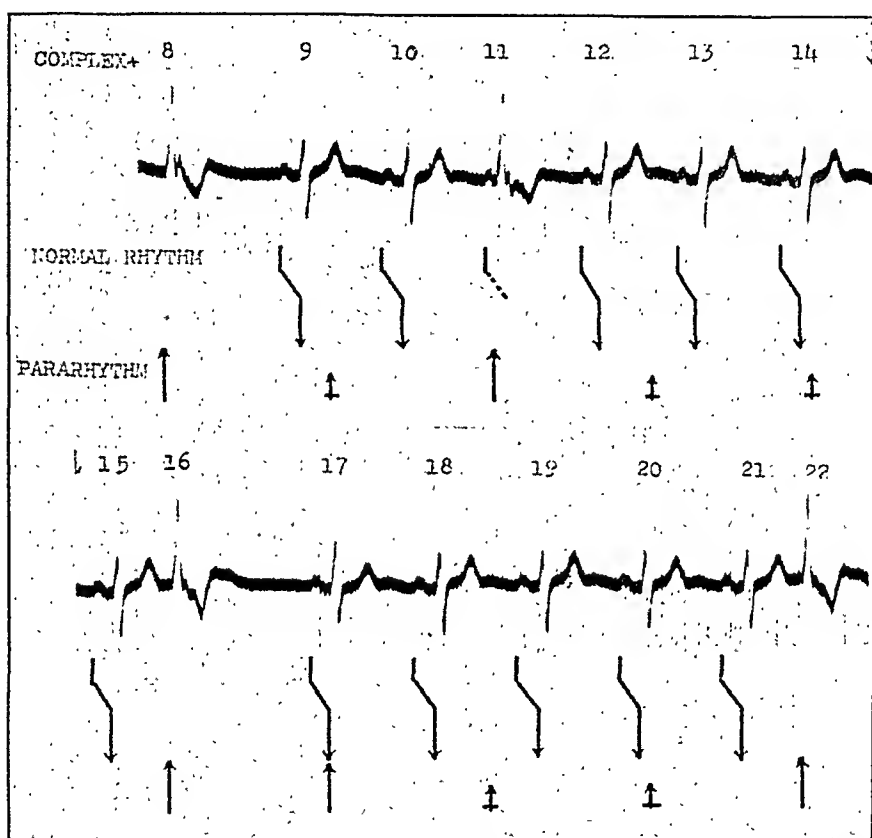


Fig. 9.—Electrocardiogram, March 1, 1935, Lead II. Complexes 8 to 22 of the film record made fifteen months after the original records. The scheme below the record represents the interplay of the two rhythms. (See text and Table II).

The shortest manifest coupling in the record was 52×0.01 second, which occurred four times. The longest latent coupling was 56×0.01 second, occurring once only. No other latent coupling exceeded 50×0.01 second. With one exception, therefore, all para-stimuli falling out with the relative refractory period produced ventricular responses, and that period in this record appears to be over 49 and under 52×0.01 second.

It seems justifiable, therefore, to conclude that a similar para-rhythm was present when this record was made. From the form of the extrasystolic complexes the ectopic focus would appear to be the

TABLE II

COMPLEX NUMBER	CONSEC- TIVE VENT. CYCLES	NORMAL BEATS: OC- CURRENCE	EXTRA- SYSTOLES: OC- CURRENCE	COUPLINGS	AVERAGE CYCLE (NORMAL RHYTHM)	AVERAGE CYCLE (PARA- RHYTHM)
1	68		68	68		
2	100	100		49		
3	80	180				
4	84	264		34		
5	80	344			85	149
6	86	430		37		
7	94	524				
8	72		596	72		
9	116	116		28		
10	92	208			92	144
11	80		288	80		
12	92	92		46.6		
13	84	176				
14	92	268		9.2	90.6	138.6
15	96	364				
16	52		416	52		
17	138	138	138	138		
18	92	230		46		
19	90	320			90.5	138
20	90	410		4		
21	90	500				
22	52	552	552	52		
23	128	128		10		
24	88	216			88	138
25	60		276	60		
26	114	114		22		
27	86	200			86	136
28	72		272	72		
29	104	104		31		
30	88	192			88	135
31	78		270	78		
32	108	108		28		
33	94	202			94	136
34	70		272	70		
35	120	120		16		
36	94	214			94	136
37	58		272	58		
38	128	128		10		
39	96	224			96	138
40	52		276	52		
41	134	134		8		
42	94	228			94	142
43	56		284	56		
44	130	130		12		
45	92	222			92	142
46	62		284	62		
47	132	132		12		
48	100	232		56		
49	104	336			100	144
50	96		432	96		
51	112	112		25		
52	94	206			94	137
53	68		274	68		
54	134	134		8		
55	98	232			98	142
56	52		284	52		

TABLE II.—CONT'D

COMPLEX NUMBER	CONSECU- TIVE VENT. CYCLES	NORMAL BEATS: OC- CURRENCE	EXTRA- SYSTOLES: OC- CURRENCE	COUPLINGS	AVERAGE CYCLE (NORMAL RHYTHM)	AVERAGE CYCLE (PARA- RHYTHM)
57	132	132		7		
58	90	222			90	139
59	56		278	56		
60	118	118		21		
61	92	210			92	139
62	68		278	68		

same as, or to have a very close anatomical relation to, that active in records made fifteen months before. The rate of discharge of stimuli bears also a close relation to the para-rhythm of the earlier record, the cycles in each varying between 130 and 150×0.01 second.

During the period of tachycardia following the exercise, the normal rhythm cycles measure 53×0.01 second. This value is sufficiently close to the relative refractory period calculated from the record to explain the absence of extrasystoles in that part of the film. Some reduction in the refractory period occurs with tachycardia, but we do not know how far this is operative in diseased or damaged heart muscle. The peculiar T-wave changes described above suggest that the recovery process in this heart was abnormal after exercise. The first isolated extrasystole, which is of similar form to the others, occurred when the normal cycles measured 88×0.01 second, but no others appeared for about a minute, extrasystoles finally appearing suddenly and in numbers with normal cycles of 85×0.01 second, and continuing to the end of the record.

SUMMARY

The case is reported of a man, aged fifty-nine years, whose electrocardiogram, taken one month after a coronary thrombosis, shewed numerous ventricular extrasystoles. The analysis of a long film record, which is given in detail in the text, shewed that these did not occur haphazardly but appeared to obey a rhythm independent of the sinus rhythm. If such an independent ectopic rhythm is postulated, all stimuli falling outwith the period during which the ventricles are refractory are effective in producing ventricular responses (extrasystoles). The case fulfills the criteria of a parasystole with simple interference dissociation. Additional evidence is afforded by the occurrence of many combination complexes, intermediate in form between the normal complexes and the pure extrasystolic complexes, and due to simultaneous stimulation of the ventricle by supraventricular and ectopic stimuli.

A record from the same patient made fifteen months later shewed extrasystoles of similar form and distribution, and an analysis of a

long film record demonstrated the persistence of a parasystolic rhythm as in the original record. The extrasystoles on this occasion, however, were not present at rest, but appeared only when the tachycardia, induced by exercise, was subsiding. The probability of some abnormality in the recovery process of this heart is suggested by the concomitant T-wave changes which occur after exercise.

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THE HEART IN EMPHYSEMA*

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IT HAS been a time-honored belief that as a result of emphysema the heart sooner or later fails. The mechanism of cardiac damage seemed obvious, for the marked distention of the lungs was thought to impede the passage of blood from the right ventricle to the left auricle. This supposition had experimental support in that the older anatomists described narrowing and destruction of pulmonary capillaries which enter into the structure of the walls of the alveoli and which necessarily must rupture when pulmonary distention becomes sufficiently great to tear lung tissue. As a result, it has been argued that an excess load is placed upon the right ventricle in its effort to force blood through the obstructed capillary bed. This, in turn, would lead to dilatation and hypertrophy of the right ventricle, and finally to heart failure. Clinically this seemed to be true, for not only were obvious signs of cardiac decompensation found commonly in elderly individuals with senile emphysema, but dyspnea, cyanosis, and dependent edema were noted frequently in younger persons with pronounced emphysema. Some investigators have believed that all patients with emphysema die of right heart failure.

This study concerns true emphysema such as follows asthma and other obstructive lesions of the bronchi. Recently it has been shown¹ that so-called "senile emphysema" is not a pulmonary disorder at all but a degenerative process in the vertebrae which leads to "barreling" of the chest. Hence, any cardiac manifestations in these cases are independent of pulmonary findings.

Recent investigations have thrown some doubt as to whether the lung distention of emphysema offers an effective obstruction to the flow of blood through the lungs.

Kretz² studied the effect of emphysema, experimentally, on the right heart of dogs. He found it difficult to obtain true values of vascular pressures within the closed thorax because of the ever changing intrathoracic pressure which is distributed evenly upon all the thoracic viscera. He concluded, however, that sufficient evidence had not been presented to warrant the assumption that emphysema alone causes hypertrophy of the right heart.

Liehteim³ attacked the problem by tying off areas of lung tissue and found that a very considerable amount of lung had to be obstructed before a rise in pressure in the pulmonary artery could be recorded.

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Kountz, Pearson, and Koenig⁴ measured the circulation time through the lungs by injecting a dye into the right heart of dogs in which emphysema had been induced. They recorded the time it took for the dye to appear in a peripheral artery and found no delay over normal dogs. Evidently there was no obstruction to the flow of blood through emphysematous lungs.

Blumgart and Weiss,⁵ by injecting a radio-active substance into the vein of one arm and measuring the time it took to detect emanations in the other arm, found that only in far advanced cases of emphysema was there retardation in the rate of blood flow through the lungs.

Heinbecker⁶ perfused the pulmonary artery and measured the rate of flow in relation to lung distention. It could thereby be shown that when the lungs were moderately distended the flow was increased due to straightening of capillaries and the opening of new ones, but when distended to a greater extent the flow was diminished.

From the above data it may be inferred that in obstructive emphysema the enlarged lungs do not materially affect the flow of blood from the right to the left heart, unless the process is far advanced, when some retardation may occur.

From the clinical standpoint, dyspnea, cyanosis, lowered vital capacity, and elevated venous pressure are all cardinal signs of both extensive emphysema and of cardiac failure. Moreover, dependent edema may be due to either condition. The mechanism of its occurrence is not certain, but two factors, namely, anoxemia and high capillary pressure, which, according to Landis,⁷ are conducive to accumulation of fluid in the tissues, are present in emphysema as well as in cardiac failure. In emphysema the anoxemia is due directly to faulty O_2 exchange between the inspired air and the blood. The elevated venous pressure has been found to depend on the rise in intrapleural pressure which influences the amount of venous blood that enters the thorax. In some cases in which edema has been observed, post-mortem examination showed greatly distended lungs and normal hearts.

It becomes, then, very difficult to recognize from clinical signs and symptoms early cardiac decompensation in the presence of obstructive emphysema. Electrocardiograms and orthodiagrams are also misleading because the heart, pulled downward by the low diaphragm, is distorted.

In view of these observations, considerable doubt arose concerning the involvement of the heart in emphysema. This was strengthened by comparative studies of series of cases wherein it was shown that patients with obstructive emphysema in whom signs usually evident in cardiac failure, as dyspnea and edema, were present, lived much longer than those with known cardiac decompensation. The post-mortem findings of normal hearts or those smaller than normal, in cases in which emphysema

TABLE I
HUMAN HEARTS

CASE NO.	BODY WEIGHT IN KG.	APPEARANCE OF HEART	HEART WEIGHT IN GM.	RATIO OF VENT. WT. TO BODY WEIGHT	VENT. WEIGHT IN GM.	RIGHT VENT. WEIGHT IN GM.	LEFT VENT. WEIGHT IN GM.	RATIO OF RT. VENT. WT. TO LT. SYMPTOMS	DURATION OF (YEARS)
1	57	Normal	260	0.00225	128	34.1	74.0	2.18	2
2	52	Normal	228	0.00271	147	44.0	87.0	1.98	10
3	62	Normal	220	0.00224	139	43.2	73.0	1.70	24
4	56	Normal	270	0.00260	145	52.0	78.0	1.50	2
5	60	Normal	325	0.00245	147	64.3	89.6	1.40	27
6	48	Normal	215	0.00260	125	38.0	52.4	1.38	3
7	50	Normal	206	0.00230	115	41.1	56.5	1.38	21
Averages	55		246.3	0.00245	135.1	45.2	72.9	1.65	14.5
8	-	Rt. vent. dil., lt. vent. hyp.	315	0.00286	166	62.4	90.3	1.45	26
9	58	Rt. vent. dil., lt. vent. hyp.	375	0.00304	177	65.0	87.4	1.34	14
10	60	Rt. vent. dil., lt. vent. hyp.	325	0.00301	181	70.1	73.6	1.05	17
11	-	Rt. vent. dil., lt. vent. hyp.	350	-	149	66.0	68.0	1.03	37
12	62	Rt. vent. dil., lt. vent. hyp.	425	0.00371	230	80.0	138.0	1.73	6
13	55	Rt. vent. dil., lt. vent. hyp.	355	0.00355	195	71.0	103.5	1.47	32
14	-	Rt. vent. dil., lt. vent. hyp.	360	-	170	68.2	98.6	1.45	2
15	58	Rt. vent. dil., lt. vent. hyp.	370	0.00343	199	71.0	101.0	1.42	25
16	58	Rt. vent. dil., lt. vent. hyp.	450	0.00345	200	77.6	97.3	1.26	21
17	-	Rt. vent. dil., lt. vent. hyp.	400	-	199	80.8	96.9	1.20	?
Averages	58.5		372.5	0.00329	186.6	71.2	95.4	1.34	22.2
Normal controls (12) averages									
(Herrmann and Wilson) 50.3			254	0.00294	146	45.8	78.6	1.73	

and the signs of cardiac failure had been present, contributed to the impression that in most cases of emphysema the heart in some way is spared. One recognized exception was the curious generalized cardiac enlargement, which has been observed from time to time in typical obstructive emphysema. In these instances damage to the heart was manifested by moisture at the lung bases, pronounced irregularities, and improvement under digitalis.

It appeared that clinical methods were not sufficiently accurate to give a clear picture of the effect of emphysema on the heart, and post-mortem reports were not very revealing since in but few cases was particular attention paid to the heart. There was no series in which measurements by weight had been made.

EXPERIMENTAL

During the past several years, we have had the opportunity of studying the hearts of seventeen autopsied cases of emphysema. In none were valvular defects present, but in a few, especially older patients, there was some degree of fibrosis in the myocardium. In seven cases the hearts appeared normal, or were distinctly small. In ten cases there was evident enlargement. In these instances a dilatation of the right ventricle was constant, and obvious thickening of the right as well as of the left ventricular wall was seen in most instances. To reduce these observations to terms of measurements, the following weights and ratios were determined: body weight, heart weight, ventricular weight, ratio of ventricular weight to body weight, right ventricular weight, left ventricular weight, and the ratio between the right and left ventricular weights. These findings were compared with similar observations on twelve normal controls made by Herrmann and Wilson,⁸ whose method of sectioning the heart was used.

The results are recorded in Tables I and I A and arranged so that the normal and the abnormal hearts are placed in separate groups. In each

TABLE I A
AVERAGE VALUES—HUMAN HEARTS

	NORMAL (7)	NORMAL CONTROLS (12) (HERRMANN AND WILSON)	RT. VENT. DIL. LT. VENT. HYP. (10)
Heart weight (grams)	246.3	(254)	372.5
Ventricular weight (grams)	135.1	(146)	186.6
Ratio of ventricular weight to body weight	0.00245	(0.00294)	0.00329
Right ventricular weight (grams)	45.2	(45.8)	78.6
Left ventricular weight (grams)	72.9	(78.6)	95.4
Ratio of right ventricular weight to left ventricular weight (grams)	1.65	(1.73)	1.34
Duration of symptoms (years)	14.5		22.2

TABLE II
AVERAGE WEIGHTS OF DRIED LUNGS—10 DOGS
(8.5 KG. TO 16 KG.)

	5 LARGE GM.	5 SMALL GM.	AVERAGE GM.	PERCENTAGE OF TOTAL LUNG WEIGHT
Right lung	15	10	12.5	55
Left lung	12	9	10.5	45
Right lower lobe	6	4.5	5.25	23
Right middle lobe	2.5	2	2.25	10
Right accessory lobe	2.5	1.5	2	8
Right upper lobe	4	2	3	13
Left lower lobe	6.5	5	5.75	25
Left middle lobe }	5.5	4.5	5	21
Left upper lobe }				

instance, hearts that appeared normal or enlarged on inspection proved to be so on measurement. The sole relation of the two groups to clinical

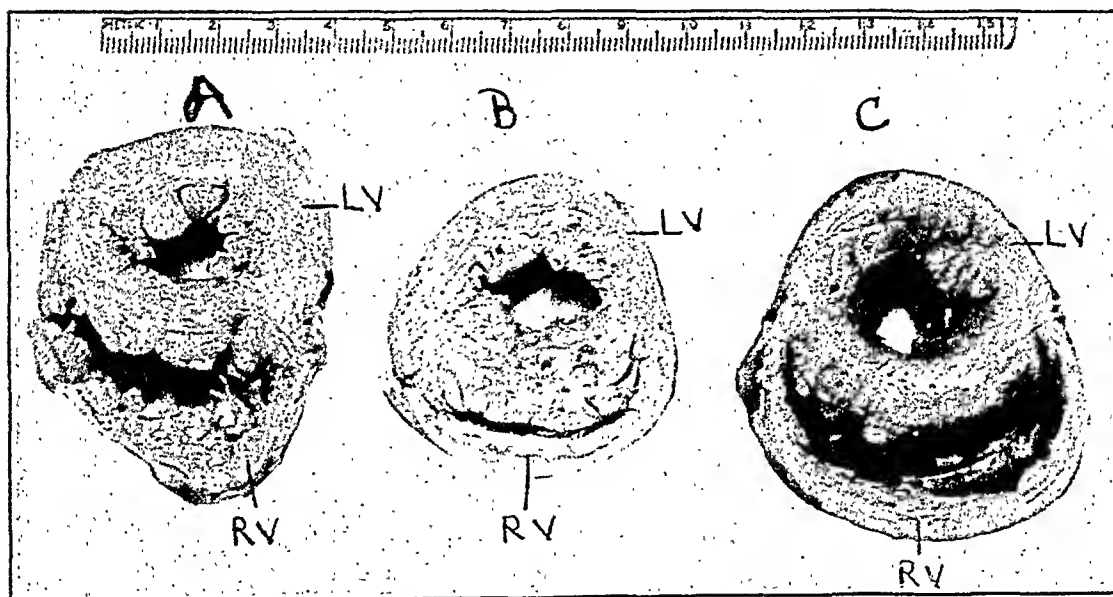


Fig. 1.—Cross-sections of hearts (A and C) from dogs with experimental emphysema. Compare with a heart (B) from a normal dog of approximately the same weight.

A and C, marked dilatation and hypertrophy of the right ventricle and hypertrophy of the left ventricle. B, normal heart. RV, right ventricle. LV, left ventricle.

data was that the average duration of symptoms in the series with hypertrophy was somewhat longer, although there are comparable individual cases in this regard in both groups. It was of interest that, in every instance in which right ventricular dilatation occurred, there was left ventricular hypertrophy. The reason for the latter finding is obscure.

To secure more information on the participation of the heart in emphysema, the process was studied in dogs. Advantage was taken of the observation of Adams,¹⁰ who produced atelectasis in dogs by painting the bronchi with silver nitrate. He noted a marked compensatory emphysema in the unaffected lobes which enlarged to fill the dead space. Although the mechanism of the production of emphysema under these

TABLE III
DOG HEARTS

DOG	APPEARANCE OF HEART AT AUTOPSY	APPROX. % OF LUNG DEST.	DURATION OF EMPH. IN MO.	RATIO OF HT. WT. TO BODY WT.	RATIO OF RT. VENT. WT. TO BODY WT.	RATIO OF LT. VENT. WT. TO BODY WT.	RATIO OF RT. VENT. WT. TO VENT. WT.	% O ₂ SAT. OF ARTERIAL BLOOD
488	Normal	45	15	0.0087	0.0023	0.0040	1.75	94
455	Normal	55	15	0.0089	0.0026	0.0042	1.62	93
155	Normal	45	19	0.0082	0.0026	0.0041	1.54	-
154	Normal	45	41	0.0074	0.0029	0.0035	1.21	-
151	Normal	45	20	0.0068	0.0024	0.0034	1.45	94
411	Normal	53	29	0.0085	0.0031	0.0041	1.33	-
488*	Normal	53	52	0.0088	0.0026	0.0036	1.25	-
486*	Normal	53	52	0.0087	0.0031	0.0035	1.14	-
Averages		50.4	30	0.00825	0.0027	0.0038	1.410	
410†	Rt. vent. dil. and hyp., lt. vent. hyp.	68	19	0.0098	0.0031	0.0040	1.32	-
152†	Rt. vent. dil. and hyp., lt. vent. hyp.	68	23	0.0090	0.0035	0.0041	1.16	-
403†	Rt. vent. dil. and hyp., lt. vent. hyp.	58	11	0.0091	0.0038	0.0047	1.24	87
400	Rt. vent. dil. and hyp., lt. vent. hyp.	80	9	0.0099	0.0038	0.0045	1.22	72
481	Rt. vent. dil. and hyp., lt. vent. hyp.	68	12	0.0130	0.0046	0.0062	1.35	90
416	Rt. vent. dil. and hyp., lt. vent. hyp.	68	26	0.0100	0.0040	0.0046	1.16	-
412	Rt. vent. dil. and hyp., lt. vent. hyp.	76	26	0.0095	0.0035	0.0042	1.21	87
409	Rt. vent. dil. and hyp., lt. vent. hyp.	68	40	0.0095	0.0032	0.0044	1.36	92
406	Rt. vent. dil. and hyp., lt. vent. hyp.	76	34	0.0097	0.0032	0.0045	1.40	60
479	Rt. vent. dil. and hyp., lt. vent. hyp.	68	20	0.0099	0.0040	0.0050	1.23	94
405	Rt. vent. dil. and hyp., lt. vent. hyp.	76	21	0.0094	0.0039	0.0040	1.03	74
Averages		70.4	21.9	0.0099	0.00369	0.00457	1.244	
Normal controls (200 dogs) (Herrmann)				0.00798	0.00265	0.00369	1.393	
Averages								

*Questionable right ventricular dilatation.

†Right ventricular dilatation prominent.

circumstances differs from the cases in man recorded above which resulted from bronchial obstruction, nevertheless the alveolar and vascular lesions in the lungs were identical in each. In order to produce considerable pulmonary distention, large amounts of lung, as much as 80 per cent, were destroyed, one lobe at a time. These were first made atelectatic and then removed surgically by successive operations. It appears that the amount of lung destruction has a definite bearing on the production of cardiac lesions, so that a method was worked out to estimate the proportion of the lung removed. This was done by weighing separately the dried lungs and the separate lobes of ten normal dogs (large and small) and estimating the percentage of each to the total lung weight (Table II).

Nineteen dogs survived the operations. The duration of emphysema was arbitrarily estimated from the date of the last operation until post-mortem examination. These periods varied from nine months to fifty-two months. When arranged into two groups, it is seen that eight hearts appeared essentially normal on inspection and eleven were pathological. Of the latter, right ventricular dilatation was prominent in all. The others showed some hypertrophy of the right and left ventricles. As with the human hearts, measurements confirmed the appearance of the organ, and again in each instance in which the heart was abnormal, both the right and left ventricles were involved. The measurements were compared with averages of the large series of controls established by Herrmann.⁹ It is recognized, however, that in that series there were wide variations and that some of the figures recorded here as pathological are duplicated in normal animals. These, however, are not sufficiently numerous to affect the averages seriously.

TABLE III A
AVERAGE VALUES—DOG HEARTS

	NORMAL (8)	NORMAL CONTROLS (200) (HERRMANN)	RT. VENT. DIL. LT. VENT. HYP. (11)
Ratio of heart weight to body weight	0.00825	(0.00798)	0.00990
Ratio of right ventricular weight to body weight	0.00270	(0.00265)	0.00369
Ratio of left ventricular weight to body weight	0.00380	(0.00369)	0.00457
Ratio of right ventricular weight to left ventricular weight	1.410	(1.393)	1.244
Amount of lung destroyed—percentage	50.4		70.4
Duration of emphysema (months)	30		21.9

DISCUSSION

The finding of cardiac damage in most of the cases studied refutes the more recent impressions that in emphysema the heart is usually not affected. How much the lesions observed contribute to clinical symptoms is debatable.

Of particular interest is the left ventricular hypertrophy which, in the absence of peripheral hypertension, cardiac infarct, myocardial degeneration, or other conditions associated with enlargement of the heart, is difficult to account for. Hoover was, perhaps, the first to discuss this problem. He suggested that, because of the faulty exchange of oxygen through emphysematous lungs, there may be a partial asphyxia of the heart muscle which would lead to increased effort and generalized hypertrophy. In this connection, it is interesting that Vaeck¹¹ was able to produce a generalized cardiac hypertrophy in mice exposed to various degrees of low oxygen tensions. Stronghold¹² induced partial asphyxia in animals and found that a reduction of oxygen in the inspired air resulted in an increase of both the diastolic volume and systolic discharge, thus increasing the work of the heart.

Hoover's theory, namely, that generalized cardiac hypertrophy is due to asphyxia, is at present under investigation and will be the subject of a further communication. Kountz and Gruber¹³ produced acute cardiac asphyxia in dogs by the injection of pressor substances, as well as by general asphyxia, and obtained a typical elevation of the S-T segment of the electrocardiogram. We have seen no such curves in patients with advanced emphysema, nor in emphysematous dogs with large hearts whose arterial oxygen content was greatly reduced by exercise. It is possible that changes in the electrocardiogram noted above are dependent upon the suddenness of the asphyxia of the heart muscle.

Geizel¹⁴ explained the generalized ventricular hypertrophy of emphysema as due to increased abdominal pressure caused by the forced descent of the diaphragm. A resistance to a large part of the peripheral blood flow would thereby be offered and the heart respond by more forceful contraction of the left ventricle. He believed that the elevated intra-abdominal pressure likewise would hasten the return flow of venous blood through the inferior vena cava to the right heart, whose intake would thus no longer be regulated by the intrapleural pressure. Geizel concluded, therefore, that both chambers of the heart would be at a disadvantage in emphysema and hypertrophy of each would occur. That this explanation is not entirely tenable is indicated by data presented below which show that when emphysema is sufficiently advanced to produce symptoms, there is probably a diminution in the amount of blood in the right auricle rather than an increase.

The left ventricular hypertrophy remains as yet unexplained. The cause of the right ventricular dilatation also is not certain. The assumption that this is due merely to the resistance offered by the reduced capillary bed in the lungs is not borne out by the experiments cited at the beginning of this paper, wherein only with very advanced emphysema does such obstruction seem to occur. Dilatation of the right ventricle has been observed in patients in whom emphysema was not of that degree.

It is entirely possible that this lesion occurs in the earlier stages of emphysema. The suggestion is based on the fact that as the diaphragm descends with the enlarging lungs the intrapleural pressure becomes more negative and the blood flow to the right heart increased. Overloading may take place at this time. Once the diaphragm is pushed down to its position of contraction and the excursion of the thorax limited by its barreling, the intrapleural pressure promptly rises, and the blood flow into the thorax becomes impeded.

This sequence of events in emphysema has been indicated by the induction of pulmonary distention in animals. In dogs, partial tracheal obstruction produced by a ball valve which offers resistance to expiration leads to marked emphysema. As the lungs distend, the intrapleural pressure falls and likewise the peripheral venous pressure. When the lungs are fully distended, the intrapleural pressure rises to be followed in a few days by rise in the venous pressure, which points to a retardation of blood returning to the heart.¹⁵ This interpretation has been confirmed by the experiments of Kountz, Pearson, and Koenig, who measured the circulation rate in dogs with emphysema and found a delay in blood flow from the periphery to the right auricle and none from the right auricle to the left ventricle. Alexander¹⁶ and his associates studied the problem in guinea pigs with anaphylactic shock during the period of lung distention. Here again, as the lungs enlarged, the intrapleural and peripheral venous pressures fell, whereas the effective pressure in the right auricle *rose*. When the lungs were fully distended, the reverse abruptly occurred—a rise in intrapleural and venous pressures and a *fall* of pressure in the right auricle, which appeared to be due to a diminished amount of blood entering the heart.

Obstruction to the flow of blood from the right side of the heart to the left brought about by diminution of the capillary bed in emphysema may contribute to the right ventricular dilatation, but only in the late stages of the disease.

As yet no explanation is available to account for the fact that in a considerable proportion of cases of emphysema, both clinical and experimental, the hearts were normal, in contrast to similar cases with cardiac damage.

SUMMARY

From these observations it appears (1) that the heart is affected in the majority of patients with emphysema; (2) that the lesion, cardiac hypertrophy, with dilatation of the right ventricle when advanced, may produce symptoms, but probably has no clinical reflection in its earlier stages; (3) that the cause of the left ventricular hypertrophy remains, as yet, undetermined; (4) that there is experimental evidence which indicates that the right ventricular dilatation and hypertrophy occur chiefly in the earlier stage of emphysema, when the lungs are in the process of distention, rather than later as generally believed.

that pellagra occurs in patients with a hypoplastic cardiovascular apparatus of constitutional origin. In the 38 cases which I am reporting, the systolic blood pressure was above 150 mm. in 5 cases (13.2 per cent), between 130 mm. and 150 mm. in 24 cases (63.1 per cent), and below 130 mm. in 9 cases (23.6 per cent).

Campbell and Allison⁶ reported eight cases of toxic polyneuritis of undetermined origin with electrocardiographic observations in three cases. These patients, in addition to the mild neuritic symptoms, had palpitation, vomiting, dyspnea on exertion, and swelling of the feet and legs. The electrocardiograms were characterized by inversion of T_1 in one case and of T_2 and T_3 in two cases. Upon recovery, the negative T-wave became positive. While these cases cannot be classified either as beriberi or pellagra, it is possible that a food deficiency was the etiological factor.

The "beriberi heart" has been studied by several investigators.⁷⁻¹¹ The electrocardiogram was normal in approximately two-thirds of the cases. In one-third of the cases low voltage, notching of the QRS in all leads, high T-waves, changing sign of T with recovery, and changes in

TABLE I
ELECTROCARDIOGRAPHIC FINDINGS

	NO. CASES	PERCENTAGE
Normal records	19	50.0
Abnormal records	19	50.0
Abnormal records without complications	14	36.8
Sinus tachycardia (90 or over)	26	68.4
Auricular fibrillation (mitral stenosis)	1	2.6
Ventricular premature beats	2	5.2
Normal voltage	37	97.4
Low voltage of QRS (below 5 mm.)	1	2.6
Large T (1, 2, or 3)	2	5.3
Pardee S-T	8 (a)	20.5
Unquestioned	(5)	
Lead I	3	
Lead II		
Lead III		
Lead III	} 4	
Inverted S-T	4	11.0
Everted S-T		
Negative T ₁	} 4 (b)	
T ₂	2	10
T ₃		
T ₃	} 4 (c)	
Abnormalities of Lead IV (apex—left leg)	12 (d)	36.4 (e)
Low voltage	3	
Monophasic S-T	2	
Upright T	10	
M complex (QRS)	1	

(a) Includes one case of aortic insufficiency and two cases of hypertension.

(b) Includes one case of hypertension and one case of mitral stenosis.

(c) Includes two cases of hypertension, one case of acute rheumatic fever, and one case of syphilitic aortic regurgitation.

(d) Includes one case of hypertension and one case of aortic insufficiency.

(e) Lead IV taken in thirty-three cases.

the P-R interval (variable) were present. These changes, while not diagnostic, tend to support the clinical findings that the heart is affected in beriberi.

Electrocardiographic Study.—Electrocardiograms were taken in all cases during the relapse of the disease and in eighteen of the cases during convalescence as well. The records were normal* in nineteen of the cases (50 per cent). In Table I are collected all of the data of the records. Careful examination of the patients revealed a number with evidence of cardiovascular disease, and reference to these findings is made in the table. The chief changes were sinus tachycardia, S-T changes similar to those described by Pardee (Fig. 1) in myocardial fibrosis sec-

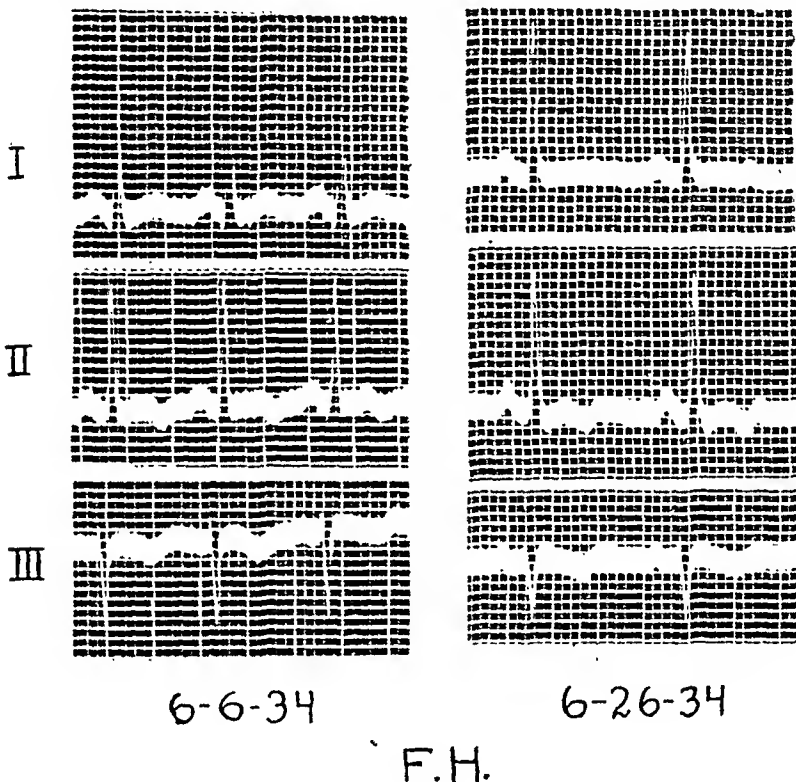


Fig. 1.

ondary to coronary disease, and inversion of T in Leads I or II or both (Fig. 2). In some instances these changes persisted, and in other cases with recovery there was a return to normal (Fig. 3). *In no case was digitalis or any drug known to affect the electrocardiogram administered.* The sinus tachycardia frequently persisted during the convalescence, and in some instances increased. Large T-waves were occasionally seen. In three cases the S-T portions of the curves were monophasic in type (Fig. 3a). The P-R interval in the thirty-eight cases varied from 0.12 to 0.21 second during the attack. In eighteen cases after convalescence was established, the P-R interval varied somewhat but not consistently. The

*Sinus tachycardia was not classified as an abnormal finding and cases were included in the 50 per cent group unless definite evidence of other abnormality was found.

QRS interval during the attack varied from 0.05 to 0.12 second and was approximately the same during the convalescence in the eighteen cases in which records were taken.

Lead IV (apex—left leg) was recorded in 33 of the 38 cases. In 12 instances this derivation was abnormal (36.4 per cent of the 33 cases). The abnormal findings are tabulated in Table I. In none of the cases with abnormal conventional records was Lead IV normal. In 4 cases Lead IV was abnormal with normal conventional leads. Progressive

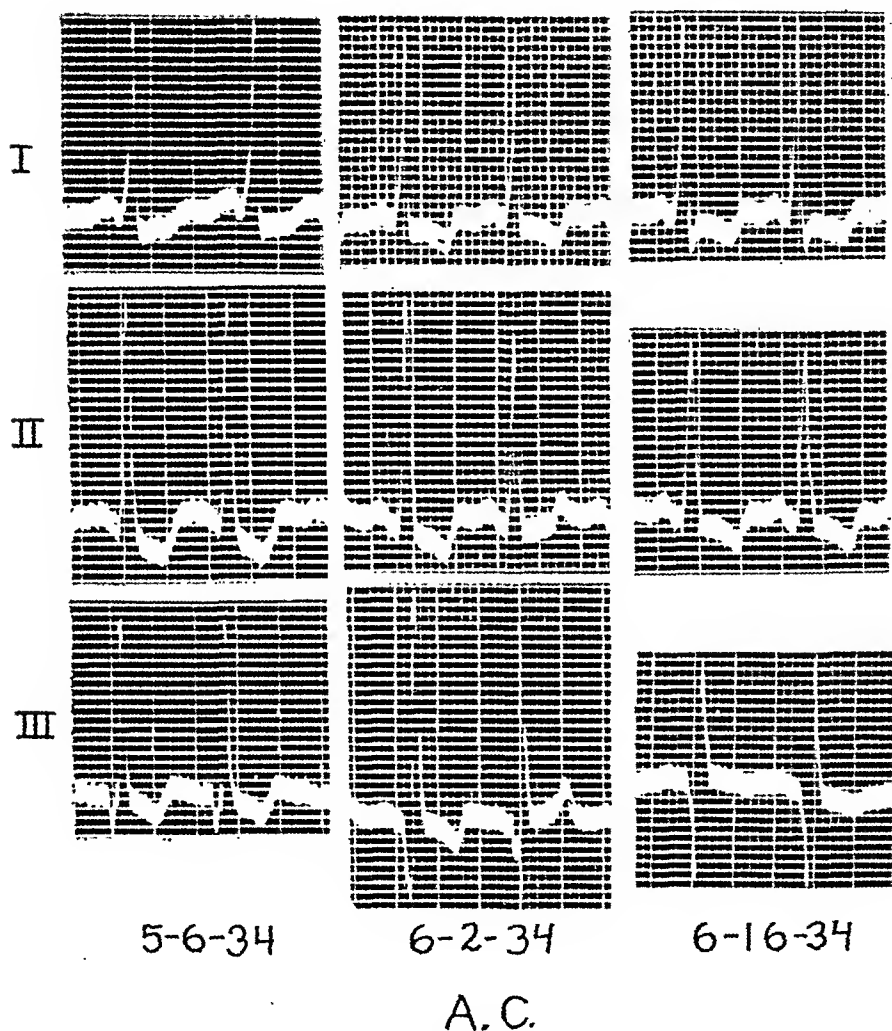


FIG. 2.

changes in Lead IV occurred in 3 cases without alterations in the standard leads, when taken during the activity of pellagra and during convalescence. In Fig. 4 are illustrated the various types of abnormal Lead IV.

The *M* QRS complex was present in Lead IV in 1 case (Fig. 4a); low voltage of the entire QRS complex was present in 3 cases (Fig. 4b), an upright T was present in 10 instances (Fig. 4c), and S-T was monophasic in 2 cases (Fig. 4d).

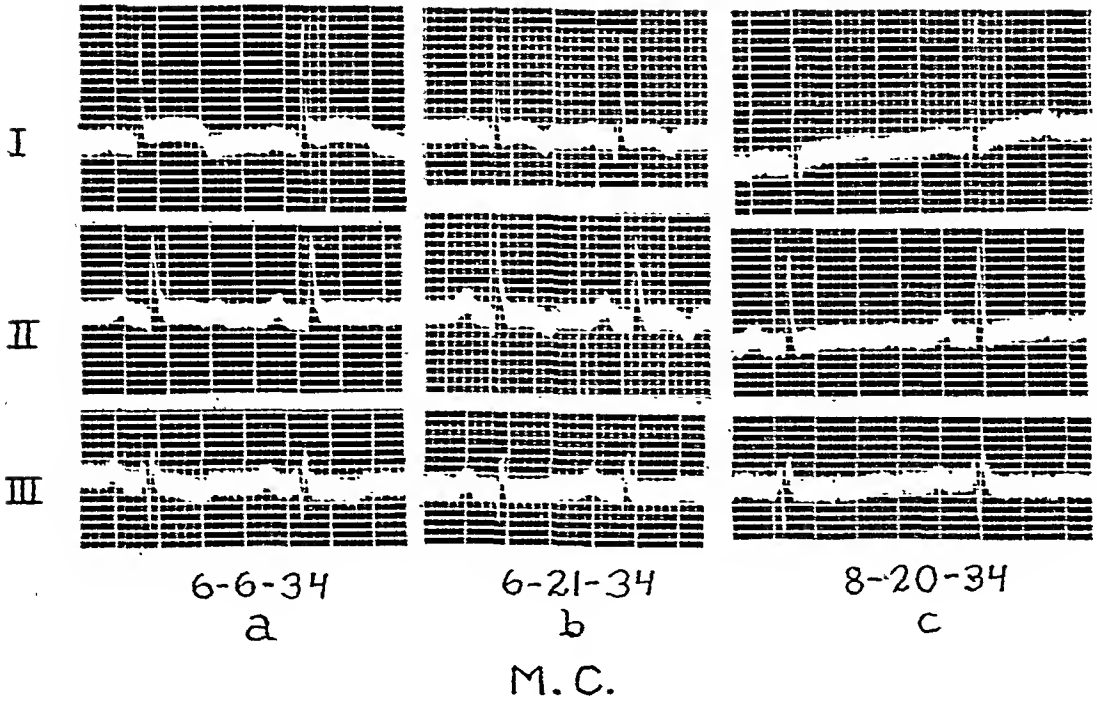


Fig. 3.

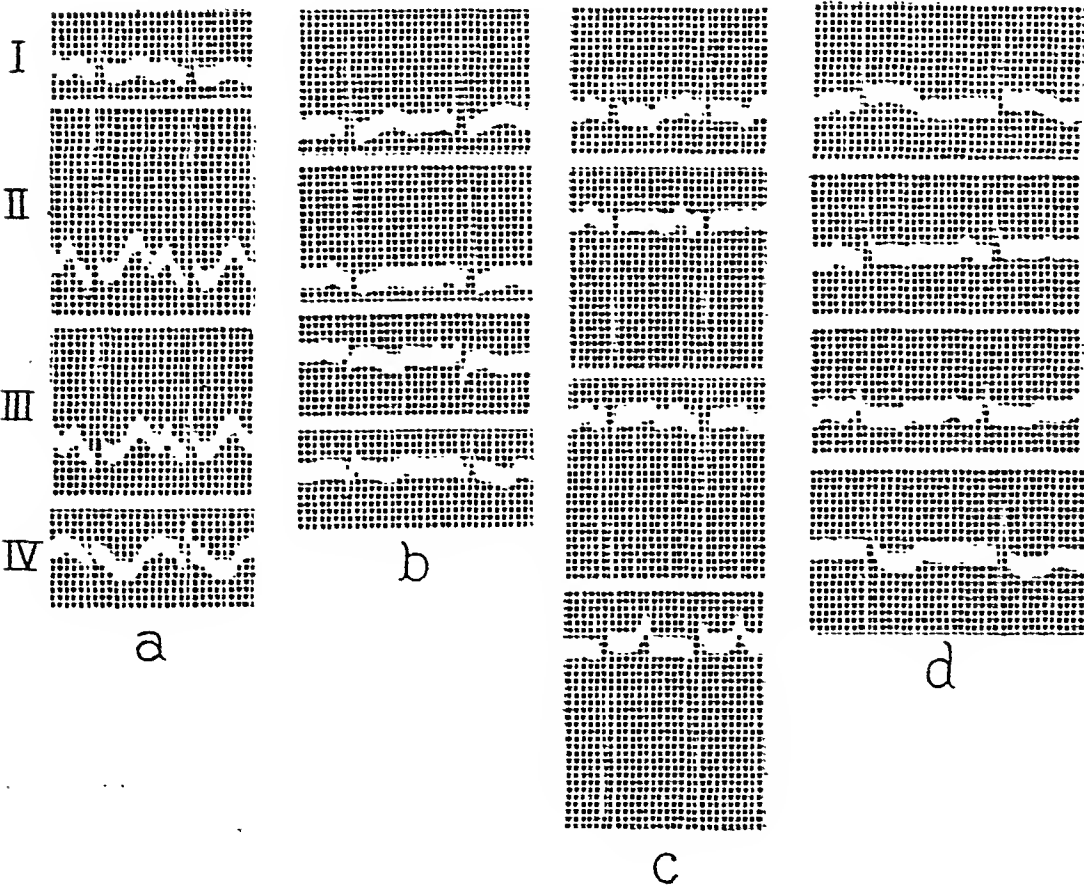


Fig. 4.

In Table II are the measurements of the P-R and QRS intervals in 18 cases during the acute stage of the disease and after convalescence was

TABLE II
MEASUREMENTS OF P-R AND QRS INTERVALS DURING ATTACK AND DURING CONVALESCENCE

PATIENT	P-R		QRS	
	ATTACK	CONVAL.	ATTACK	CONVAL.
M. C.	0.19	0.17	0.09	0.07
G. B.	0.14	0.14	0.08	0.08
A. C.	0.14	0.14	0.12	0.11
P. G.	0.14	0.13	0.07	0.07
W. H.	0.19	0.19	0.10	0.07
R. L.	0.14	0.18	0.07	0.06
A. L.	0.14	0.13	0.07	0.07
B. L.	0.14	0.14	0.09	0.09
L. S.	0.16	0.16	0.05	0.06
C. K.	0.21	0.22	0.06	0.06
G. P.	0.12	0.14	0.07	0.06
C. C.	0.16	0.16	0.06	0.07
E. H.	0.14	0.14	0.07	0.05
A. C.	0.14	0.16	0.08	0.08
A. S.	0.11	0.14	0.07	0.08
W. C.	0.18	0.14	0.09	0.07
E. F.	a. f.	0.20	0.07	0.09
M. B.	0.15	0.15	0.09	0.07

TABLE III
ELECTRICAL SYSTOLE

PATIENT	PELLAGRA SEVERE			CONVALESCENT		
	CYCLE SEC.	RATE	Q-T	CYCLE SEC.	RATE	Q-T
M. C.	0.78	77	0.39	0.53	113	0.31
G. B.	0.84	71	0.38	0.53	113	0.29
A. C.	0.62	97	0.37	0.55	109	0.36
P. G.	0.75	80	0.42	0.57	105	0.36
W. H.	0.88	68	0.46	0.91	66	0.43
R. L.	0.86	70	0.38	0.79	76	0.38
A. L.	0.79	76	0.37	0.57	105	0.26
B. L.	0.49	123	0.34	0.49	123	0.34
L. S.	0.70	86	0.32	0.75	80	0.34
C. K.	1.03	58	0.41	1.05	57	0.40
G. P.	0.70	86	0.35	0.64	81	0.35
N. K.	0.56	107	0.33	0.77	78	0.39
R. R.	0.47	128	0.30	0.45	133	0.31
E. S.	0.80	75	0.40	0.57	105	0.34
A. S.	0.77	78	0.37	0.60	100	0.24
F. B.	0.53	113	0.34	0.55	109	0.35
A. C.	0.76	79	0.38	0.60	100	0.32
E. F.	0.57	105	0.36	0.67	82	0.37
F. H.	0.48	125	0.27	0.65	92	0.32
E. H.	0.53	113	0.34	0.48	125	0.26
C. H.	0.69	81	0.38	0.74	70	0.39

well established. The Q-T interval was measured in three consecutive cycles in each record and the averages recorded on the graphs (Figs. 5 and 6.) The normal controls* were obtained from measurements of

*From the same age group.

electrocardiograms of young normal adults by Dr. R. A. Shipley and Dr. William R. Hallaran.¹² The normal subjects are recorded as solid dots and the pellagrins as circles. The diagonal lines were drawn to show the limits of normal. In all instances, systole (Q-T abscissae) was plotted against cycle length (ordinates). Both graphs show that there

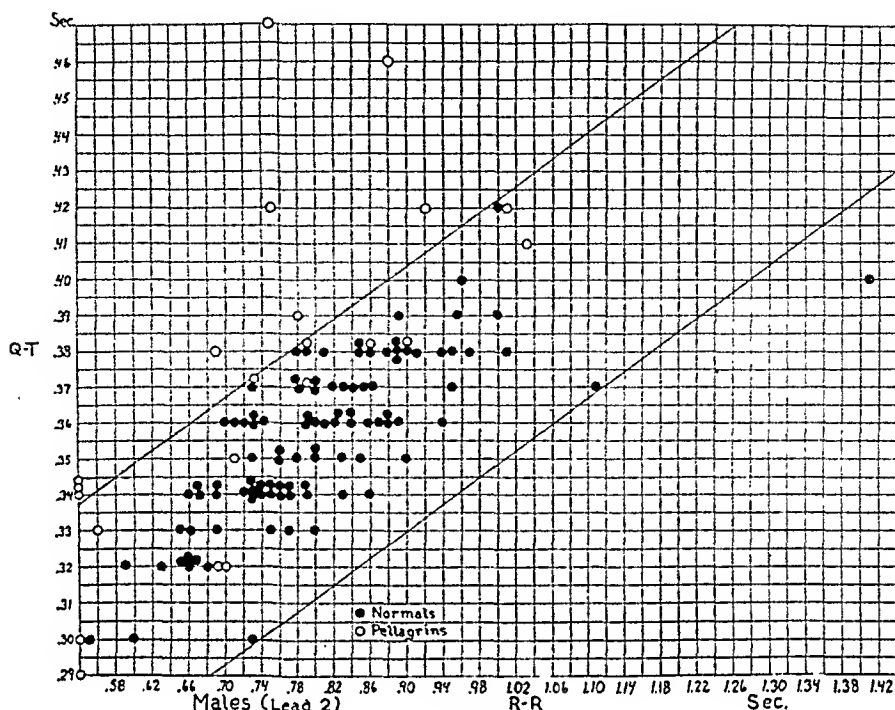


Fig. 5.

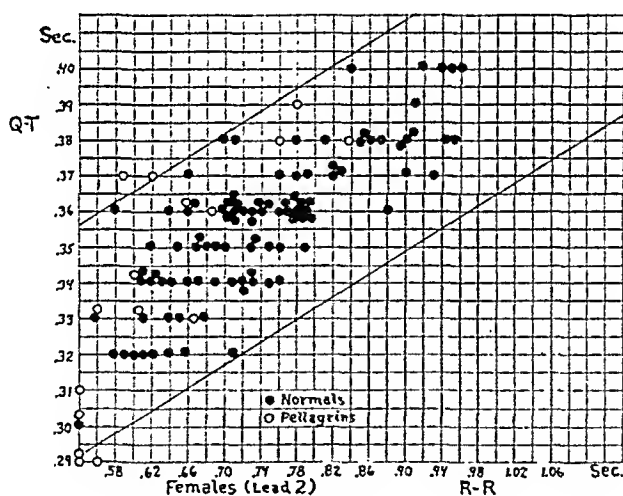


Fig. 6.

is a tendency for systole to be prolonged, especially with slower rates. Observations made after recovery show that in many instances Q-T is shortened. This change was found to be true in both male and female patients. Table III is a complete record of these observations. When the average Q-T was determined by the formula of Cheer and Dieuaide¹³ $Q-T = K \sqrt{C}$ (Q-T and C in seconds and K a constant) it was found that

the average value of K for the male pellagrins was 0.437 (normal $K = 0.397^*$) and for the females 0.430 (normal $K = 0.415^*$).^{*}

In eleven instances, electrical systole was shortened during recovery; it was unchanged in three instances and was lengthened in seven cases.[†] Because of the frequent variation in heart rate, these figures cannot be studied without taking the cycle length into consideration. Figure 7 was constructed by plotting the duration of Q-T of the individual observations against cycle length (R-R). The solid dots represent Q-T before treatment and the circles after treatment in twenty-one cases.

Alcoholism and the Electrocardiogram.—Nine patients suffering from alcoholism but without evidence of pellagra were studied electrocardiographically. In all cases the records were normal. The P-R, the QRS, and the Q-T intervals were measured (Table IV), and in all instances these intervals were found to be within normal limits. In six of these cases, records were taken after all signs of alcoholism had disappeared and when the patients were ready for discharge from the hospital. The Q-T interval was unchanged in all of the cases.

TABLE IV
MEASUREMENTS OF P-R, QRS, AND S-T IN ACUTE ALCOHOLISM WITHOUT EVIDENCE OF PELLAGRA

PATIENT	HEART RATE	P-R		QRS		Q-T	
		ALCOHOLISM	CONVAL.	ALCOHOLISM	CONVAL.	ALCOHOLISM	CONVAL.
J. C.	63 77	0.17	0.16	0.07	0.05	0.38	0.36
A. M.	93	0.14		0.06		0.31	
E. C.	73 110	0.14	0.14	0.06	0.04	0.34	0.28
O. N.	96 102	0.14	0.14	0.04	0.06	0.32	0.32
E. S.	80 90	0.17	0.17	0.05	0.05	0.36	0.36
C. T.	83	0.14		0.06		0.33	
R. F.	88	0.14		0.06		0.35	
C. F.	90 100	0.18	0.18	0.06	0.06	0.34	0.34
J. C.	90 100	0.13	0.13	0.05	0.05	0.33	0.32

Other Possible Factors Causing Changes in the Electrocardiogram.—There is a possibility that metabolic factors such as low blood calcium (as in deficiency of parathyroid hormone) and changes in water balance and in the acid-base equilibrium, play a rôle. These factors are being investigated by Dr. Tom D. Spies.

*Y, normal range of K for males: 0.337 to 0.433; Z, normal range of K for females: 0.380 to 0.456 (Normal series of Shipley and Hallaran).

†The prolongation of mechanical and of electrical systole was not limited to the group with hypertension.

In summary, Q-T is frequently prolonged in pellagra, and, when the cycle length is considered, there is frequently an abbreviation during convalescence.

The Phases of Systole (Mechanical Systole).—Simultaneous records of heart sounds and the subclavian pulse were recorded photographically by the method described by Wiggers,¹⁴ and the phases of systole

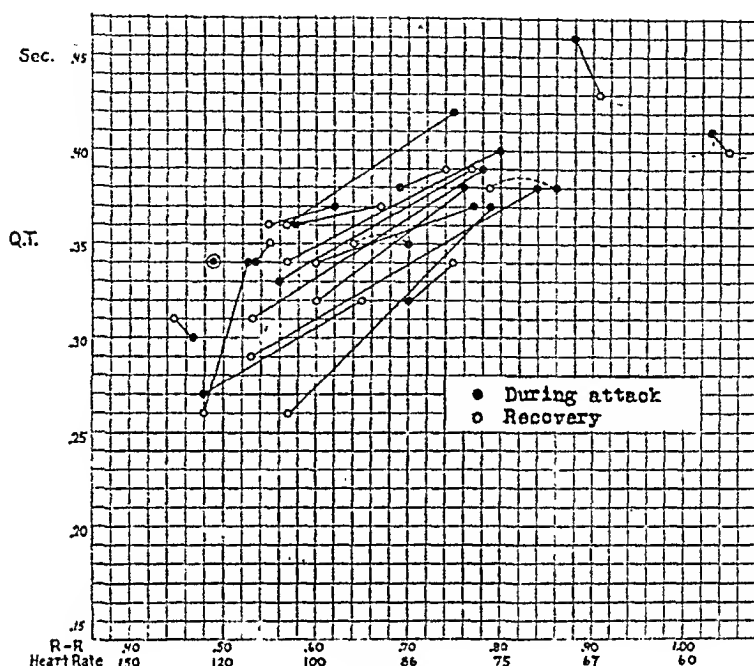


Fig. 7.

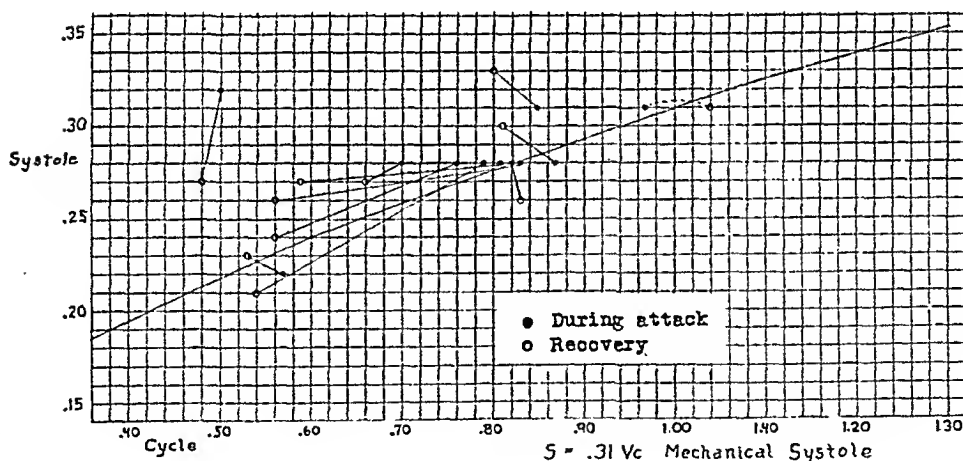


Fig. 8.

were computed by a method described by Katz and Feil.¹⁵ In twelve patients, observations were made during the acute stage and after convalescence began. Table V is a complete summary of the figures of the isometric and ejection phases and of total systole with corresponding cycle lengths. When the recorded systole is compared with the calculated systole ($0.31 \sqrt{C}$), it is seen that systole was prolonged in five cases and abbreviated in but one instance. During convalescence

systole was prolonged in seven cases, the same in one case, and shortened in two instances. When systole during the disease is compared with systole during convalescence and plotted against cycle length, the frequent abbreviation of systole during convalescence is made clear (Fig. 8). It may be concluded then that pellagra tends to prolong mechanical systole and that recovery frequently reduces this interval. The isometric phase varied from 0.04 to 0.09 second during the attack and from 0.05 to 0.11 second after the attack. No consistent change occurred in individual cases. The ejection phase was reduced in six cases during convalescence. The changes in the duration of systole were due to changes in ejection time.

TABLE V
MECHANICAL SYSTOLE

PATIENT	CYCLE LENGTH		RATE		ISOMETRIC PHASE		EJECTION PHASE		TOTAL SYSTOLE		$s = 0.31 \sqrt{c}$	
	ac.	con.	ac.	con.	ac.	con.	ac.	con.	ac.	con.	ac.	con.
M. C.	0.79	0.54	76	111	0.05	0.05	0.23	0.16	0.28	0.21	0.275	0.228
G. B.	0.83	0.56	72	107	0.06	0.06	0.22	0.19	0.28	0.26	0.282	0.232
A. C.	0.57	0.53	105	113	0.06	0.05	0.16	0.18	0.22	0.23	0.234	0.227
P. G.	0.76	0.56	79	107	0.04	0.06	0.24	0.18	0.28	0.24	0.271	0.232
W. H.	0.87	0.81	69	74	0.04	0.07	0.24	0.23	0.28	0.30	0.288	0.279
R. L.	0.85	0.80	71	75	0.07	0.10	0.24	0.23	0.31	0.33	0.286	0.276
A. L.	0.81	0.59	74	101	0.08	0.09	0.20	0.17	0.28	0.27	0.278	0.237
B. L.	0.50	0.48	120	125	0.08	0.11	0.15	0.16	0.32	0.27	0.219	0.215
L. S.	0.83	0.83	72	72	0.09	0.08	0.19	0.19	0.28	0.26	0.280	0.282
C. K.	0.97	1.04	62	58	0.08	0.08	0.23	0.24	0.31	0.33	0.304	0.316
G. P.	0.70	0.66	86	91	0.08	0.05	0.20	0.22	0.28	0.27	0.259	0.252
C. C.	0.69	0.74	87	81	0.05	0.10	0.20	0.23	0.25	0.33	0.257	0.267

NOTE.—Electrical and mechanical systole were not always concomitantly prolonged.

Pathological Findings.—Twelve patients dying of pellagra were studied pathologically, but only one of this group had electrocardiograms and observations on the duration of the phases of cardiac systole. The hearts were examined in all cases macroscopically and microscopically by Dr. Francis Bayless. No gross changes were noted, nor were there significant changes in the microscopic sections. The heart weights of fourteen autopsied cases are recorded in Table VI. Of the six females the heart weight was below the average normal weight in four cases and slightly increased in two instances. In both of these cases the blood pressure was within normal limits (M. M. and A. J.). Of the eight males the heart weights were increased in two instances, in both of which the blood pressure was within normal limits (J. S. and H. D.). One patient had arteriolar nephrosclerosis in addition to pellagra, but elevation of blood pressure was the only clinical evidence of the disease. The heart of this patient, a colored male of forty-five, weighed 340 gm., and the myocardium was normal both macroscopically and microscopically. There were small arteriosclerotic plaques on the intima of the large coronary vessels, but no narrowing of the lumina was present.

TABLE VI

HEART WEIGHTS IN POSTED PELLAGRINS WITH AVERAGE BLOOD PRESSURE READINGS

PATIENT	SEX	AGE IN YR.	HEART WEIGHT IN GM.	B.P.
M. M.	F.	30	370	118/ 82
A. J.	F.	30	320	100/ 76
C. W.	F.	24	230	140/ 98
P. P.	F.	26	165	80/ 60
H. P.	F.	33	205	90/ 60
C. J.	F.	27	230	126/ 88
J. S.	M.	62	440	118/ 84
R. B.	M.	36	290	135/ 90
T. G.	M.	79	300	145/105
H. D.	M.	37	420	130/115
A. G.	M.	65	300	110/ 60
M. C.	M.	45	340	170/126
H. P.	M.	52	370	144/100
A. M.	M.	45	340	184/104

Röntgenographic Findings.—In a number of cases teleroentgenograms were taken during and after the attack. The heart was usually normal (unless valve lesion or hypertension was present). There was no deviation from the normal contour of the silhouette.

DISCUSSION

Acute pellagra is frequently associated with cardiovascular symptoms: subjectively, dyspnea on effort and palpitation; and objectively, tachycardia, feeble heart sounds, and slight edema in some instances. The prolongation of electrical systole and the frequent lengthening of mechanical systole may be the expression of abnormal cardiac function. The electrocardiogram was abnormal in 36.8 per cent of thirty-eight clinical cases of pellagra without complications. This figure may be compared with the figure of Keefer¹¹ in beriberi (37 per cent). Pellagra and beriberi apparently affect the heart physiologically in much the same way. The cardiac manifestations in pellagra, however, are less severe. Acute alcoholism was not responsible for the electrocardiographic changes seen in the pellagrins.

SUMMARY

In this study of 38 patients with moderate to severe pellagra, electrocardiographic abnormalities in the ventricular complex occurred in 50 per cent. In 14 of these 19 patients there was no complication which might alter the electrocardiogram (36.8 per cent). The chief abnormalities were inversion of T in Leads I or II or both, Pardee type of S-T, and large T-waves. Lead IV was abnormal in 12 instances out of 33 cases in which it was recorded (36.4 per cent). Lead IV was abnormal in 4 cases with normal Leads I, II, and III. The Q-T interval and mechanical systole were prolonged in some cases. These findings

suggest that the heart is affected physiologically in pellagra. Twelve hearts (one of which was studied electrocardiographically and dynamically) examined pathologically showed no gross or microscopic abnormality. Roentgenographic changes were lacking in the cases studied.

Thus it may be concluded from these clinical, electrocardiographic, and dynamic studies that the heart is affected by pellagra.

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ELECTROCARDIOGRAMS ON 167 AVERAGE HEALTHY INFANTS AND CHILDREN*

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THE 1,276 electrocardiograms which form the basis of this study were taken on 167 healthy children, of whom 85 were boys and 82 were girls. They ranged in age from three weeks to twelve years. The majority of these (115) form a group of average healthy children of the community who are being followed from birth to maturity. They are brought in the first time during the third or fourth week of life and every month for the first three months, then at approximately three-month intervals for so long as we are able to follow them, the oldest now being over 12 years of age. The routine consists of complete physical examinations, roentgenograms of chests, sinuses, spines, wrists, heads and teeth, electrocardiograms, anthropometric measurements, basal metabolism tests, with dental checks every six months and psychometric, social, and behavior studies once each year. Careful family histories and records of the prenatal and newborn periods are obtained, and all additional departmental findings, information, and reports are subsequently added. The "Special Series" of 52 was not started at birth, but they have been referred to us for special reasons and have been followed in the same manner.

The electrocardiographic study was started five and one-half years ago. Our records represent repeated electrocardiograms on the same children for this period of time. The greatest number of records on one child is seventeen, with an average of 7.6 records on each child. The records of two of the "Birth to Maturity Series" have been dropped from this study as there was a question as to whether or not they were in average health.

RÉSUMÉ OF LITERATURE

In 1908 Funaro¹ under the direction of Nicolai and at Heubner's suggestion made the first electrocardiograms on infants and children. Only Lead I was taken on forty-five children. They found S_1 frequently deep. Heubner² a little later in that year also noted the deep S_1 . He also called attention to the small or absent R-wave in the first lead in infants. In 1913 Hecht³ took a group of seventy children consisting of premature infants, newborn infants, and young and older children, but all were not normal. At different periods he found

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S_1 less than R_1 in different subjects. P_1 was found split once, and R and S split more frequently especially in older children. The T-wave was small in infancy and inconstant in Lead III at all times.

In 1913 Noeggerath⁴ studied a series of sixty-eight normal (?) children, taking only Leads I and II.

In 1917 Krummbhaar and Jenks⁵ presented their studies on forty-two normal subjects whose ages ranged from immediately after birth to eleven years. They found that a right preponderance was present until the second or third month and by the sixth month the infant's electrocardiogram had become practically the same as that of the adult. R_2 became greater than R_3 about the sixth week, but S_1 persisted abnormally large for several months; Q-wave, prominent throughout their series, especially Q_2 and Q_3 ; T-wave, absent for the first week and after the first three weeks reached a "proportionate size," and largest and frequently inverted in Lead III; and the P-R interval, shorter than in the adult.

In 1920 electrocardiograms were taken by Seham⁶ on 101 normal children from one hour to thirteen years of age. He found that the P-wave was higher in childhood than in the adult; Q-wave, deeper than in the adult, and added confirmatory evidence that there is a right ventricular preponderance in the first few months of life, R, generally much higher than in the adult; S_1 , deeper in the first three months than in any other period of life and in other leads relatively deeper than in the adult; T, frequently absent in the first ten days of life and after that quite constant; T_1 , more regular than T_2 and T_3 which was inverted in 15 per cent of the cases between six and thirteen years; and the transmission time, on the whole, shorter than in the adult.

In 1928 Brughaard and Wurnerlich's⁷ studies consisted of 115 electrocardiograms on premature infants, newborn infants, and older infants. That same year Lincoln and Nicolson⁸ published their study of 222 normal school children from three to twelve years of age. They established a series of normal figures for each age period, with standard deviations. They showed the possible sex and family characteristics and stressed the difference between the tracings of an adult's heart and a child's heart. They found that the P-, R- and T-waves were higher than in the adult and the transmission time shorter. The Q- and S-waves were not constant and decreased with age, this decrease being most marked in Q_3 , while S_3 showed an irregular increase in depth from year to year, and T_3 was inverted in 35.5 per cent of their cases. An average of 62 per cent of the children showed a sinus arrhythmia.

In 1931 Shookhoff and Taran's⁹ series of 259 normal children from six to fourteen years of age was published. P_2 was split, diphasic, or inverted in 17.6 per cent of the cases in Lead III. A widening and

a slight slurring of QRS interval in Lead III was seen in 34.8 per cent; and T_2 was inverted in 24.8 per cent of their cases.

TECHNIC AND PROCEDURE

The first twenty-two records used in this study were taken with a string galvanometer type of machine. Technical difficulties encountered in taking records of infants and younger children directed us to the beam galvanometer.* With the exception of these twenty-two early records all were taken on this machine. In several of the early records the same child had electrocardiograms taken on both machines, one record succeeding the other. It was found that both checked very well. Standard electrocardiographic methods were used throughout; namely, 1 cm. of deflection of string or beam for 1 millivolt introduced into the circuit and the three customary arms and leg leads. Outing flannel bands with pockets, moistened in warm saline solution, were used to apply the electrodes.

An endeavor was made to quiet the child, but nothing further was attempted, and conditions were similar in every way to those existing in the physician's office. The infants up to seven months of age were taken lying in a crib. From that age to three years six months in boys and three years in girls 158 records were taken in the sitting position while 325 were taken in the supine position. In the first group when the child moved too much in the lying position, he was allowed to sit up alone or in his mother's lap, rubber aprons being used to insulate the parent so that we could get a measurable record. Of those taken in the sitting position there were only seven tracings which established the high or low limits in amplitude for a given wave within one age group. This was checked by a change from the supine to sitting posture at a later date. In only one instance was there a change in that particular wave whose amplitude had previously been high or low.

These electrocardiograms were interpreted according to accepted standards. In the discussion to follow, reference will be made to adult standards which unless otherwise stated will refer to standards of the Heart Committee.¹⁰

With this brief introduction on technic and procedure, we present our observations on the amplitude and form of each individual wave and the intervals and rhythms encountered.

THE P-WAVE

Amplitude.—In our series higher and lower amplitudes were found than in the adult, considering the upper limit as 2.5 mm. and the lower limit as 0.5 mm. High amplitude was more marked in the girls

*Through the courtesy of the General Electric Corporation we were allowed the use of a Victor Electrocardiograph.

TABLE I
AMPLITUDE MEASUREMENTS OF THE P, Q, R, S, AND T WAVES BY PRECEDING AND PRESENT AUTHORS

WAVES	AUTHORS	AGE	3 WK. TO 6 MO.		7-12 MO.		13-18 MO.		19-24 MO.		2-3 YR.		3-4 YR.		4-5 YR.		5-6 YR.		6-7 YR.		7-8† YR.	
			RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.
P	Krumhaar and Jenks ⁵	I mm.	0-1.5		1		1		1		2						1.5		2		2	
		II	1-2		1		1		1-2		2						2		3		2	
		III	0-1		0		1		0.5-1		1						?		1		1	
	No. of ECG.*		15		1				3		1						1		1		1	
		I	0-1.5		0-1.5		0-1		1-2		1		0.4-0.5		1-1.5		1-1.5		1-1.5		0.5-2	
		II	0-2		0-2		0-2		1-2		1		0.5-2		0.5-3		2-3		0.5-2.5		1.5-2	
	No. of ECG.*		26		8		5		2		2		2		3		3		5		4	
		I											0.5-2		0.5-3		0-3		0.5-3		0.5-3	
		II											1-4.5		1-3		0-3.5		0.5-3.5		0.5-3	
		III											0-3.5		0-3		0-3		0-2.5		0-3	
Q	No. of ECG.*												9		40		57		58		68	
		I											0.5-2		0.5-3		1.3		0.5-3		0.5-3	
		II											1-4.5		1-3		0-3.5		0.5-3.5		0.5-3	
	Present series												0.5-2		0.5-3		1.3		0.5-1.8		0.5-2	
		I	0.5-2	0.97	0.5-2	0.96	0.5-2	1.3	0.3-2	1.0	0.5-1.5	0.97	0.5-2	1.0	0.5-2	0.95	0.5-1.5	0.98	0.5-1.8	0.92	0.5-2	1
		II	0.5-2	1.2	0.5-3	1.4	0.5-2	1.3	0.5-3	1.4	0.5-2	1.3	0.85-2	1.2	0.5-3	1.3	0.5-2.5	1.2	0.3-2	1.2	0.3-3	1.1
	Burnett and Taylor		0.2-2	0.76	0-2	0.77	0.3-1.5	0.75	0.3-2	0.8	0.3-2	0.75	0.2-1	0.7	0.2-2	0.7	0.3-1	0.7	0.2-1	0.6	0.2-1	0.67
		III	178		140		84		87		146		129		100		81		81		80	
		No. of ECG.*																				
	5	I mm.	0-6		0		1		0-3		0						2		0			
		II	0-6		3		6		0-6		2						1		0.5			
		III	1-10		6		1		2-4		3						3		3			
6		I	0-2		0-1		0-1.5		0-1		0-1		0.5-1		0-1.5		0-1		0-1			
		II	0-3		0-2.5		0-4		1		0.5-2		0-0.5		0-0.5		0-1		0-2			
		III	0-4		0-1.5		0-5		2		1		0		0-1.5		0-0.5		0-3			

*The figures for the number of electrocardiograms at each age period remained the same for each wave and are not repeated.

†Figures for the ninth through the eleventh years are not included in this table as the small number of individual cases did not justify an average.

‡For differences between boys' and girls' ranges-see charts in Figs. 1, 2, 3, 5, and 6.

TABLE I—CONT'D

AVERAGES	AUTHORS	AGE LEADS	3 WK. TO 6 MO.		7-12 MO.		13-18 MO.		19-24 MO.		2-3 YR.		3-4 YR.		4-5 YR.		5-6 YR.		6-7 YR.		7-8+ YR.	
			RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.
8		I																				
		II																				
		III																				
Present series		I	0-3	0.3			0-2.5	0.28	0-6	0.57	0-4	0.4	0-4	0.5	0-4	0.4	0-4	0.34	0-1.5	0.16	0-1.8	0.26
		II	0-7	1.4			0-6	1.4	0-5	1.2	0-3	1	0-3	0.95	0-5	1.1	0-4	0.92	0-4	0.6	0-2	0.6
		III	0-10	2.9			0-8	3.4	0-7	2.4	0-7	2.3	0-4.5	1.9	0-5	1.3	0-4	1.6	0-4	1.4	0-3	1
5	R	I mm.	3-18				6		1-9		6						9		12		16	
		II	7-18				8		10-13		7						12		14		13	
		III	5-14				9		6-8		6						5		4		3	
6		I	1-6				3.5-11		0.4-10		4		3		4-6		5-7		5-9		2-8	
		II	0-10				4-17		7		7-7.5		5-12		6-12		6-8		7-22		7-11	
		III	1-15				4-10		4-6		5-5.5		2-6		4-6		2-5		0-21		4-8	
8		I											5.5-15	9.9	6-20	10.4	4-16.5	9.9	5-16	9.5	5-18	9.7
		II											8-32	15.9	8-23	14.3	4-26.5	15	6-25	13.7	7-24	12.3
		III											5-31	10.9	2-23	10.5	2-24	11.2	3-24	10.6	3-26	10.5
Present series		I	1-14	6.2			3-17	7.6	2-17	7.9	2-16	6.9	2-17	6.4	2-15	6	2-12	5.6	2-14	6	2-13	5.5
		II	1-20	10.2			2.5-24	11.1	1-19	11.4	2-19	11.2	3-23	11.8	3.5-19	12.1	3.5-25	12.2	5-30	12	4-24	12.5
		III	1-20	9.5			2-17	8.3	1-18	8	1-17	8.4	2-17	8.5	1-19	9.7	2-20	9.8	1-27	8.9	1-19	9.4
5	S	I mm	2-11				2		3-7		4						2		2.5		0	
		II	1-5				0		0-5		2						1		1		0	
		III	0-16				0		0-3		0						0		3		0	

TABLE I—CONT'D

WAVES	AUTHORS	AGE LEADS	3 WK. TO 6 MO.		7-12 MO.		13-18 MO.		19-24 MO.		2-3 YR.		3-4 YR.		4-5 YR.		5-6 YR.		6-7 YR.		7-8† YR.	
			RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.
6		I	1-8		0-3.5		0-2		2		0-1.5		0.5-1		0-4		0-3		0-3		0-4	
		II	0-8		0-3		0-3.5		2		0-2		0.2-3		1.5-4		1-4		0-2		1.3-4	
		III	0-8		0-2.5		0-1.5		1-2		0-0.5		0.5-1		0-2		2-4		0-2		0-1.5	
8		I											0-6.5		0-6		0-4.5		0-7		0-5	
		II											1-7		0-5		0-7		2		0-5	
		III											0-7		0-4		0-5		0-9		0-7.5	
Present series		I	0-15†	4.2	0-11	4	0-13	6	0-8	3.2	0-13	2.9	0-6	2.3	0-7	2.3	0-7	2.5	0-9	2.2	0-8.5	1.8
		II	0-6	2	0-9	2.1	0-6	1.7	0-7	1.8	0-6.5	1.9	0-5	1.6	0-5	1.4	0-5	1.3	0-9	1.7	0-6	1.6
		III	0-5	1.2	0-8	3.8	0-9	6	0-9	1	0-7.5	0.76	0-8	0.93	0-8	0.7	0-8	0.75	0-6	0.8	0-7	0.9
5		I mm	1-6		3		4		2-7		3						1.5		3		4	
		II	1-5		2		2		1-4		3						2		2		4	
		III	0-5		1		2		1-2		1						?		1		1	
6		I	0-3		0-2		1-6		2-3		1		2		3-5		2-4		4-5		2-7	
		II	0-6		1-3		1-5		1.5-3		2		4-5		3-4		2-6		3-6		3-9	
		III	0-5		0-1		0-2		0-2		0-1		1		1-1.5		3		1-4		2-4	
8		I											2-5		1-6		0-6.5		1-6		1-6	
		II											1-7		3.4		0.5-7		0-5.5		1-6	
		III											1-4		0-2.5		0-4		0-5.5		0-4.5	
Present series		I	0.5-7	2.3	0.5-6	2.8	1-6	2.7	1-6	3	1-6	2.7	1.5-5	2.9	1-5	2.7	1-5.5	3	1-6	2.8	1-6	3
		II	0.7-6	2.7	1-7	3.2	1-6	3.2	1-6.5	3.2	1-7	2.8	1.5-6	3.2	1-7	3.2	1-7	3.6	1-6	3.3	2-8	3.9
		III	0-4	0.91	0-3	1.1	0-4	1.2	0.3-3	1.1	0.5-3	1.2	0.2-3	0.91	0.2-2	0.96	0.2-3	1	0.2-3	0.98	0.2-1	1.3

than in the boys. As shown in Fig. 1, in girls the upper limit of 3 mm. was observed in four age groups while 2.5 mm. was noticed only once in boys. Further it shows the variation in range was less evident in Lead III than in the other two leads. After the tenth year there appeared to be less variation in all leads, especially in Lead I. For amplitude measurements as observed by other workers see Table I.

Notching, which first appeared in the third and fourth years, was noted in 195 or 15.2 per cent of our records. P_1 was notched in 42, or 3.2 per cent; P_2 in 49, or 3.8 per cent; and P_3 in 104, or 8.15 per cent; of the electrocardiograms. A number of previous workers^{3, 6, 8, 9} report a split or notched P-wave as occurring in childhood. There are likewise several references to this occurrence in the adult electrocardiograms. This has been mentioned frequently as associated

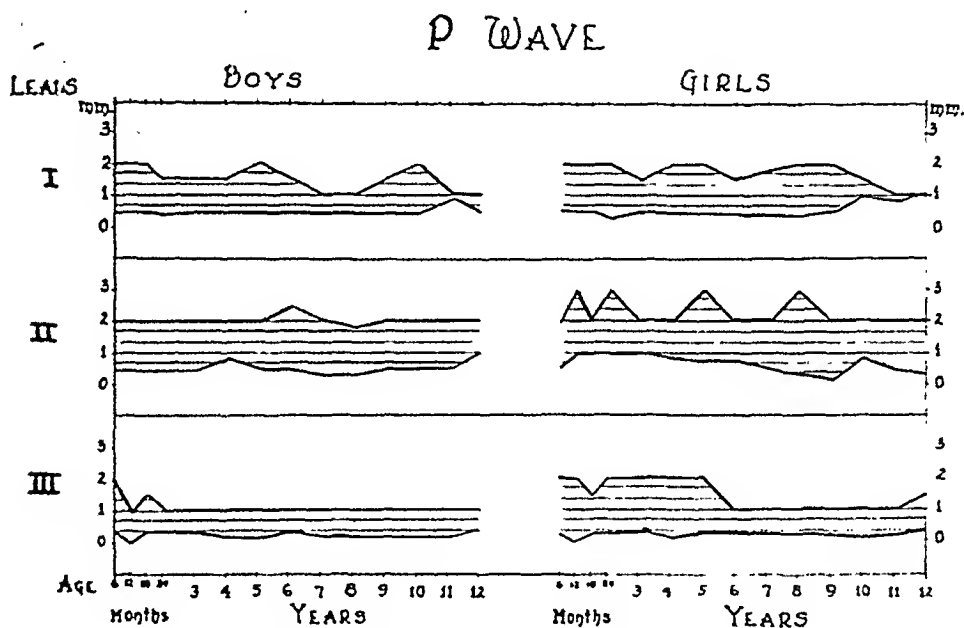


Fig. 1.—Amplitude range in P-wave.

with rheumatic heart disease, especially in the presence of mitral stenosis. Pardee¹¹ appears to be uncertain as to its meaning in the adult electrocardiogram. We would point out that the occurrence of notching of the P-wave in 15.2 per cent of average healthy children casts added doubt upon this finding as indicative of a lesion of the mitral or any other valve.

Diphasic forms which paralleled the notching were observed in P_2 in 6, or .047 per cent, and in P_3 in 46, or 3.6 per cent, of our records. Inversion of P_3 which appeared in the earliest records and throughout the series was noted in 133, or 10.4 per cent, of our records. After form changes in the P-wave had once appeared, we were unable to observe any age in which they were especially evident.

Summary.—The P-waves showed higher and lower amplitudes than in the adult and were more frequently high in girls than in boys.

However, the average of all waves in the three leads throughout the age period did not show any notable departure from the averages observed in the adult electrocardiogram.

Diphasic forms occurred in Leads II and III and notched forms in all leads. Inversion which occurred only in Lead III was found in the earliest records and totaled 133, or 10.4 per cent, in the entire series.

THE Q-WAVE

The Q-wave, representing the beginning of the ventricular complex, is not always present but is quite often seen in the electrocardiogram of early childhood. In our series the Q-wave when present was deeper in all leads in boys than in girls and diminished with age. Q_3 was

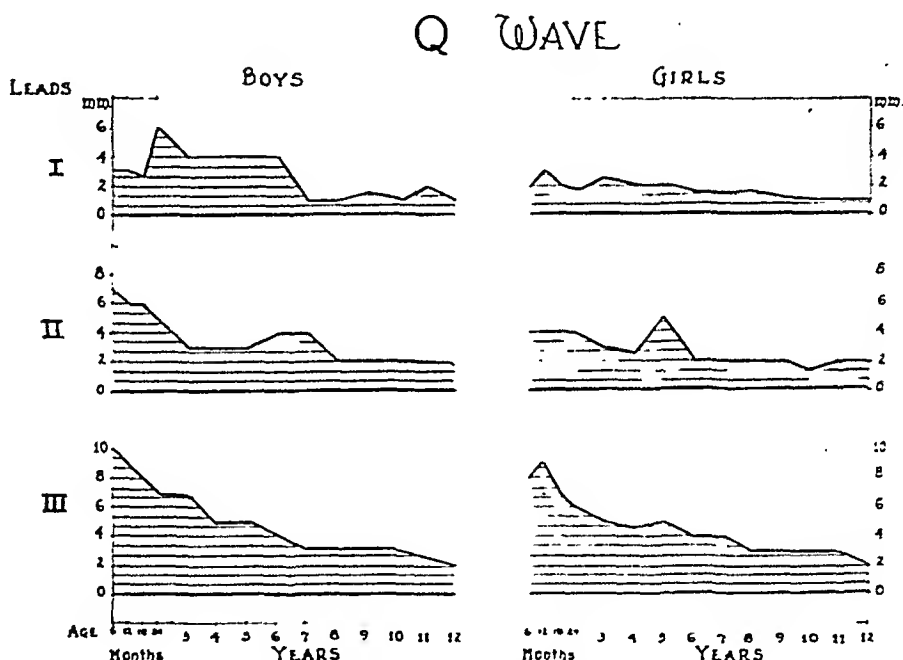


Fig. 2.—Amplitude range in Q-wave.

greater than Q_1 and Q_2 . Both facts agree with the data of Lincoln and Nicolson.⁸ In Leads I and III a marked decrease came at seven years in the boys while the decrease in the girls was more gradual. Q_3 showed slurring and notching in three electrocardiograms.

Reference to Fig. 2 will show the observed amplitudes of Q-waves in the three leads. In our series of normal electrocardiograms the Q-wave frequently exceeded in amplitude 25 per cent of the largest upward deflection of the QRS complex shown in any lead—the criterion employed in determining abnormally large Q-waves in the adult electrocardiogram.¹¹

Summary.—The Q-waves diminished with age and were slightly deeper in boys than in girls. Q_3 showed the most gradual decrease in amplitude. Large Q-waves occurred in average healthy children.

THE R-WAVE

The R-wave is the main upward deflection of the ventricular complex. Linetsky¹² found that in adults the R-wave became higher with age and with increase of heart size. Previous workers, already cited, have shown the tendency for R-waves to be higher in the child than in the adult. For detailed amplitude measurements of these authors see Table I.

Amplitude.—Our records (Fig. 3) show that the R-wave observed in any given electrocardiogram may occasionally be lower or higher

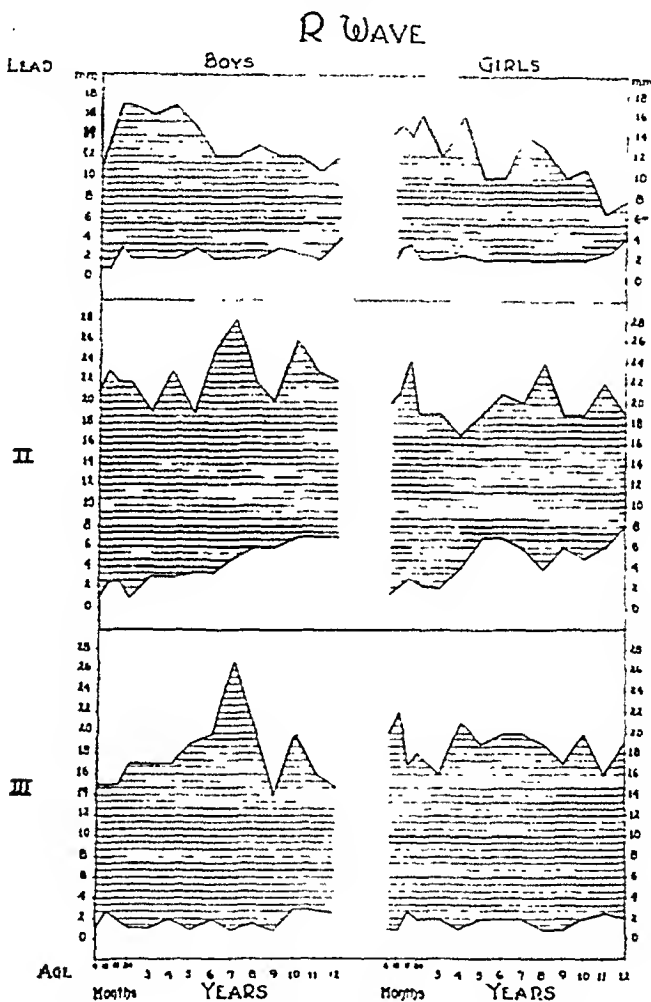


Fig. 3.—Amplitude range in R-wave.

than the usual adult standards. (Heart Committee,¹⁰ 5 mm. to 20 mm.; Pardee,¹¹ 7 mm. to 17 mm.; Burnett and Piltz,¹³ 8 mm.) Out of our entire series 137 records representing 55 individual cases were 17 mm. or over, while 98 records representing 44 cases were 7 mm. or below, the lowest being 3 mm. in two cases. Our curves show that when high or low R-waves were present in one record there was a tendency for the successive records to show the same thing. In boys the range of variation seemed to be somewhat greater than in girls but without any significant age difference. The average figures show that R_2 was

higher than R_1 or R_2 . Waxing and waning, i.e., at least a 2 mm. variation in the height of the R-wave, was found in 69, or 5.4 per cent, of our series.

Slurring and Notching.—The term "slurring" is used whenever a thickening of either limb of the R-wave occurs clearly separated from the base line. R_1 was slurred 145 times, or in 11.1 per cent of our series. In 21 of these records R_2 or R_3 was also slurred. Of 87, or 6.8 per cent, showing slurring in R_2 , 20 showed slurring in an additional lead while 67 showed slurring in only this lead. R_3 showed the largest number of variations. It was slurred in 225 records, or 17.6 per cent; out of which 31 records showed slurring in two other leads.

The term "notching" is used when there is a definite spike in any portion of the wave not adjacent to the base line. This was found in 7 records in Lead I, in 4 records in Lead II, and in 45 records in Lead III. In some records R_3 was notched in one complex with an M or W form in another.

M and W Forms of QRS Waves and Their Modifications.—Throughout this study we have used this term to apply to R- or S-waves which were so notched as to present roughly an M or W appearance. We did not lay down any exact criterion as to the height or depth of this complex or whether all were above or all were below the base line. Since the completion of the study of these curves, we have noted a report by Edeiken and Wolferth¹⁴ on this form of QRS complex in which the authors have employed rather rigid criteria. We then made a somewhat limited search of various works on this subject and were surprised to find that a term so generally used appears to our knowledge in only one text, namely, in Neuhof's,¹⁵ and that his criteria agree with ours. Neuhof presented some experimental evidence that purely physical factors may account for this type of split waves and that alone they should not be used as evidence of myocardial disease in the adult. In our series M - or W -form R_3 -waves were noted in 35, or 2.7 per cent, of our records. The succeeding records may have been notched, M or W form, or possibly changed to an inversion of the R-wave.

Inversion of R-Wave.—The objection to this term is recognized, but at least in records of the age periods under discussion we are unable to advance a better term. In many of these records the chief downward deflection seems to be neither Q nor S. Inversion of the R-wave occurred only in Lead III and was present in 23, or 2 per cent, of our electrocardiograms. One hundred and twenty-four, or 9.7 per cent, of our records which showed notching, M or W forms, or inversion of R_3 were taken on thirty-five boys and nineteen girls. This indicates that the presence of one of these forms may be followed by one

or more of the associated forms in subsequent records. In nine cases the R_s was found under two of the above classifications while in four cases under all three.

In Fig. 4 we present various modifications of the M and W forms. In *a* we show the customary form; in *b* the M and W appearance is less evident, but on comparison with curves in *a* there is a marked similarity. In *c* the QRS complex does not impress one as belonging to either form, and yet comparison with *b* shows a likeness. In all of these we are unable to classify accurately the various components of the

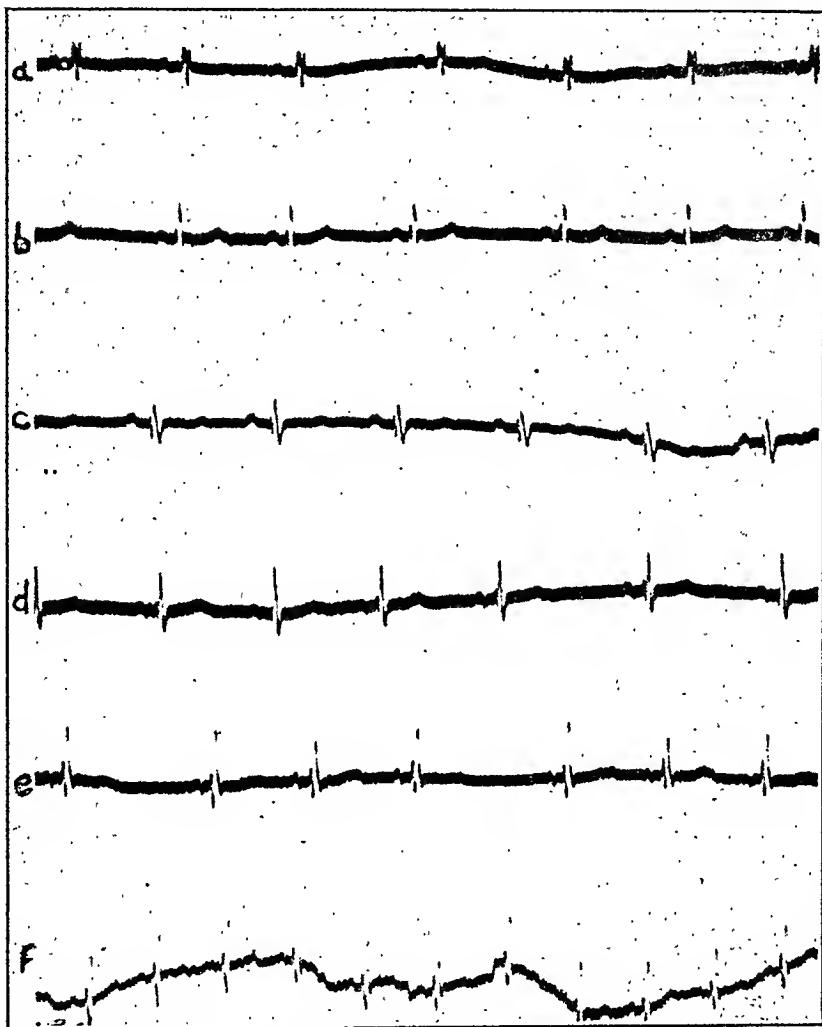


Fig. 4.— M and W forms of the R -wave and their modifications.

complex. How should one classify the first upward wave if the succeeding downward deflection is a Q -wave, or are we dealing with an inversion of all waves? If this explanation is adequate, there would be one remaining deflection unaccounted for. In addition to these changes, we show some variations in which M or W forms are not evident, but in which there is continuously or intermittently an extra and unclassified deflection. In *d* there is inconstantly an upward deflection preceding the R -wave. In *e* and *f* this is more marked, and in *f* succeeded by a deep Q -wave which shows rhythmical increase in depth.

Pardee¹¹ in his latest edition describes these variations in the QRS complexes. He prefers the term "vibratory" since many of these do not approximate closely an *M* or *W* and considers these not uncommon in Lead III.¹⁶

Wiggers¹⁷ occasionally noted this "initial splintering" in normal adults and attributed this to "slightly unequal excitation of the two ventricles, the bio-electrocardiograms of which do not fuse into one smooth groove." The relative size changes are due to changes in the electrical axis with respiration. He labels these split or diphasic initial complexes and does not attach any significance to them.

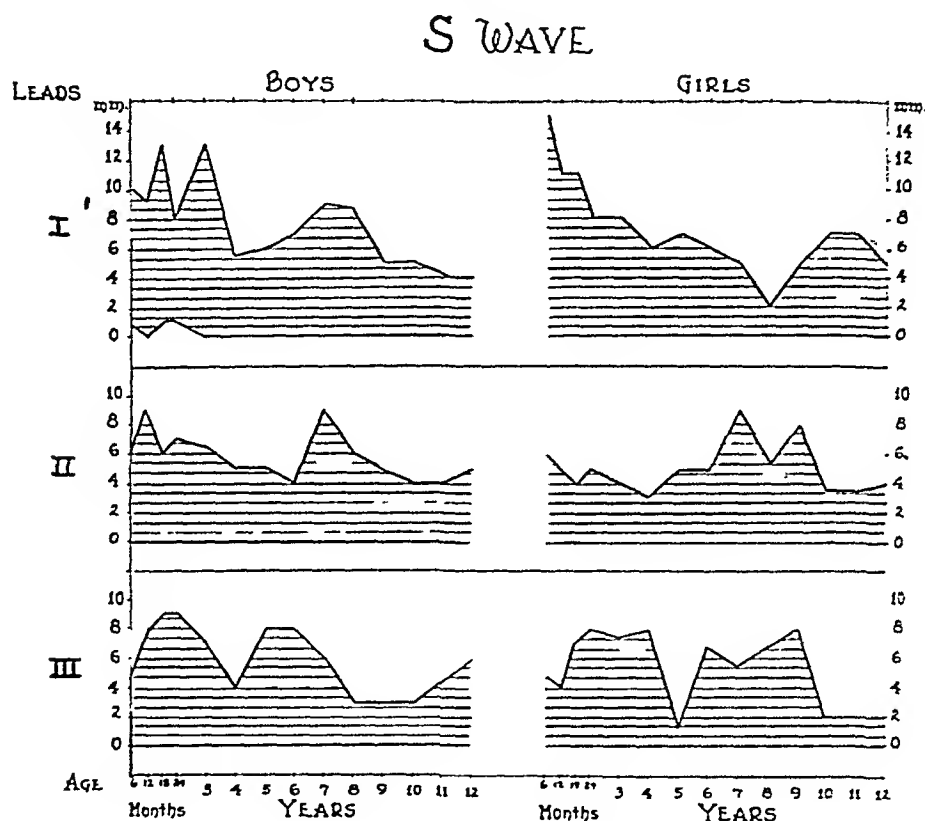


Fig. 5.—Amplitude range in S-wave.

Wilson¹⁸ finds that they are difficult to classify or label but feels that the QRS group must be treated as a unit and that the letters *Q*, *R*, and *S* are to be used separately only for the purpose of description.

McGinn and White¹⁹ discussed this inconsistency of nomenclature in a "Note on Nomenclature" in a study of the duration of the QRS complex. They suggest that the QRS wave may be described as consisting of plus and minus deflections extending so many millimeters above or below the base line without any arbitrary and often misleading attempts to label the individual deflections by exact letter. This method has the merit both of simplicity and accuracy.

Summary.—All R-waves may be higher or lower than in the usual adult standards. R-waves showed slurring in 457, or 35.8 per cent,

and notching in 56, or 4.3 per cent. *M* and *W* forms (2.7 per cent) and inversions (2 per cent) of R_3 were observed. It was difficult to classify portions of the QRS complex.

THE S-WAVE

Our series (Fig. 5) shows a decrease in size with age in boys and girls in all leads, but most marked in Lead I. Minor variations in amplitude occur independent of age or sex. The suggestion of Lincoln and Nicolson⁸ regarding an increase in left ventricular activity shown by S_3 increase is not confirmed by our series. S_1 was slurred eleven times in our series and S_3 in six records, while Lincoln and Nicolson noted S_3 notched in twenty-two cases and split in six cases. (See Table I for amplitude measurements of other authors.)

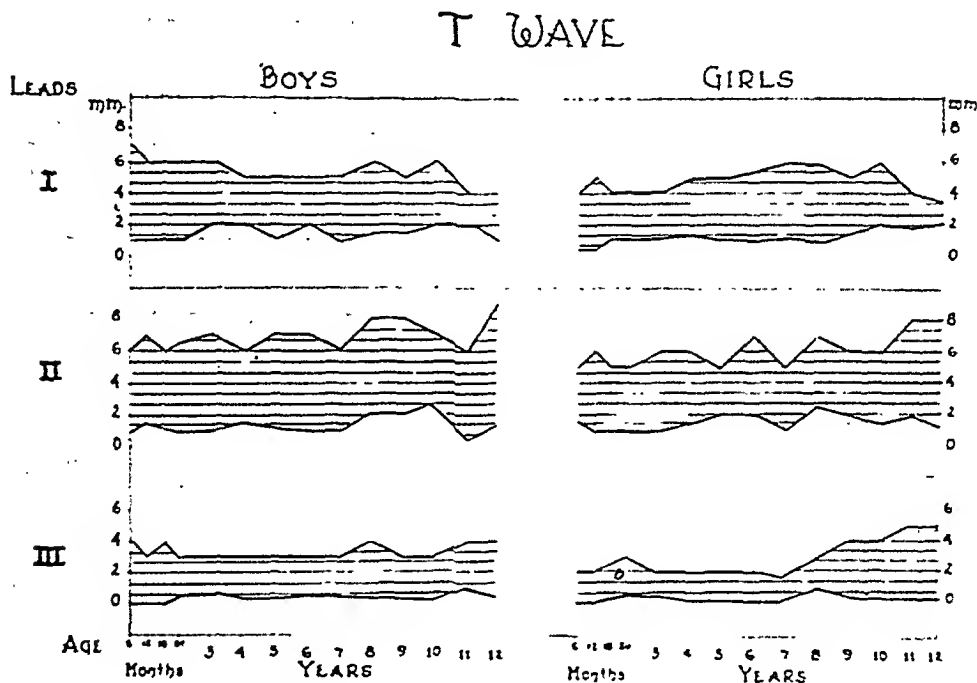


Fig. 6.—Amplitude range in T-wave.

THE T-WAVE

Our observations beginning with three-week-old infants show a well-defined T-wave in Leads I and II and usually in Lead III although of low voltage. (See Table I for comparison of figures of other authors.)

In our series Lead I was similar in both boys and girls but was usually higher than the adult standard of 5 mm. This was more marked in Lead II where it reached an amplitude of 8 mm. both in boys and in girls. T_3 was in general somewhat lower in both. These facts may be observed in Fig. 6.

In early, middle, and late childhood and adult life the T-wave, especially in Lead III, may show susceptibility to external influence. In our series there are several records in which T_3 became inverted

when the child changed from the recumbent to the sitting position. This change in posture probably has an effect upon the heart similar to that which occurs when there is a "shift to the right" since the mediastinal structures are extremely flexible at this age. Winteritz²⁰ believes that T_2 inversion in the adult indicates pronounced right heart hypertrophy, but most observers attach only slight if any importance to inversion occurring solely in Lead III in the adult electrocardiogram; certainly the T-wave in the adult is much less stable than the other deflections. A study of the electrocardiographic changes with shift in position is being made and will be subsequently reported.

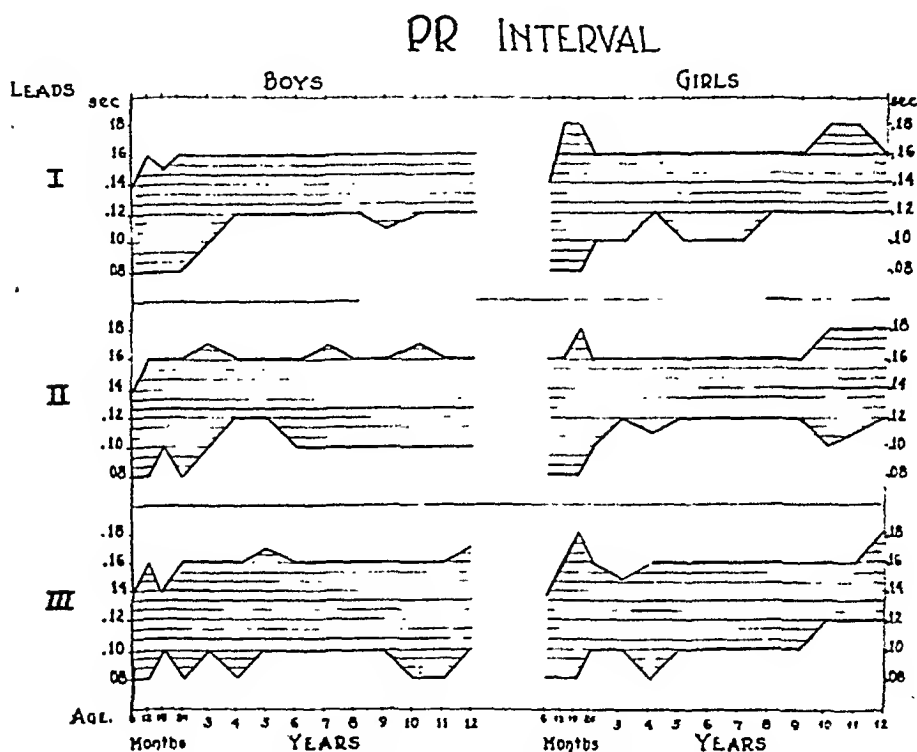


Fig. 7.—Variations in P-R intervals.

Forms.—Lincoln and Nicolson⁸ have described the following forms of the T-wave: (1) a fairly steep rise from the R-S complex with a blunt peak and an abrupt drop; (2) the wave arising immediately from the R or S terminal at the base line with no S-T interval; and (3) the origin of the T deflection starting directly from the descending limb. All of these forms appeared in our series.

An inverted or a diphasic T-wave occurred only in Lead III. Inversion was seen in 242, or 18.9 per cent, of our records. Of these 140 were from boys and 102 from girls. The maximum frequency was found in the fourth and fifth years, with a decrease until the eleventh year. A diphasic T_2 was seen in only ten records.

Summary.—Well-defined and high T-waves were observed in Leads I and II. T_3 was usually of low voltage. Inversion was found only in T_3 . It appeared in 242, or 18.9 per cent, of the records.

THE P-R INTERVAL

A more rapid conduction time for children than for adults and an average of 0.136 second have been noted by previous authors.^{3, 6, 8} An average of our series for the first eight years gave the slightly lower figure of 0.126 second. The extremes in the duration of the P-R interval at different age periods in boys and girls may be seen in Fig. 7 as 0.16 and 0.17 second, except in two instances in the second and third age group when one girl showed a duration of 0.18 second. In the later age groups all leads in girls approximated 0.18 second.

QS INTERVAL

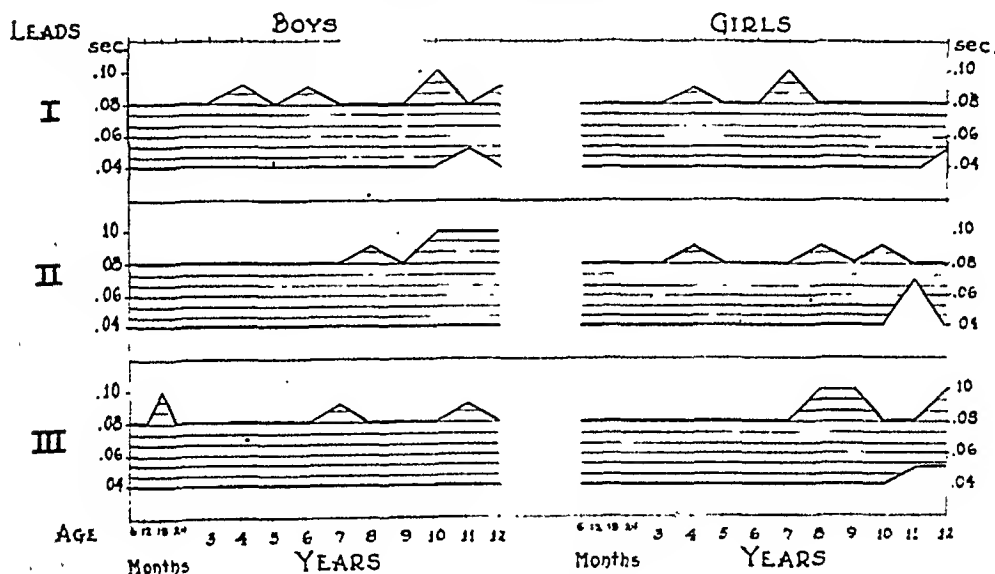


Fig. 8.—Variations in Q-S intervals.

This interval varies in different leads from this high point to as low as 0.08 second. These shorter intervals seem to bear no relation to sex or age. No explanation for this is advanced.

Summary.—The auriculoventricular conduction time varied from 0.08 to 0.18 second and averaged 0.126 second for the first eight years.

THE Q-S INTERVAL

Previous reports^{8, 6, 19} showed this conduction time from 0.06 second, upper limit 0.09, with no significant age difference. In our series (Fig. 8) a range of 0.04 to 0.08 second was usually found in this interval while adult standards are 0.081 to 0.10 second. However, 0.10 second was the upper limit in several age groups and appeared to bear no relationship to age or sex. The average in our series for the first eight years was 0.0549 second.

Summary.—The Q-S transmission time was shorter in the hearts of children.

THE S-T INTERVAL

A very definite age factor was found in the length of the S-T interval. This is seen on comparing Fig. 9 with Figs. 7 and 8. In the early age groups the range was from approximately 0.16 second to 0.28 second, whereas at the twelfth year it was from 0.24 second to 0.34 second. The lengthening of this interval was due obviously to a lengthening of systole at the later age periods. From a study of the Figs. 7, 8, and 9, it is evident that conduction time from the sinus

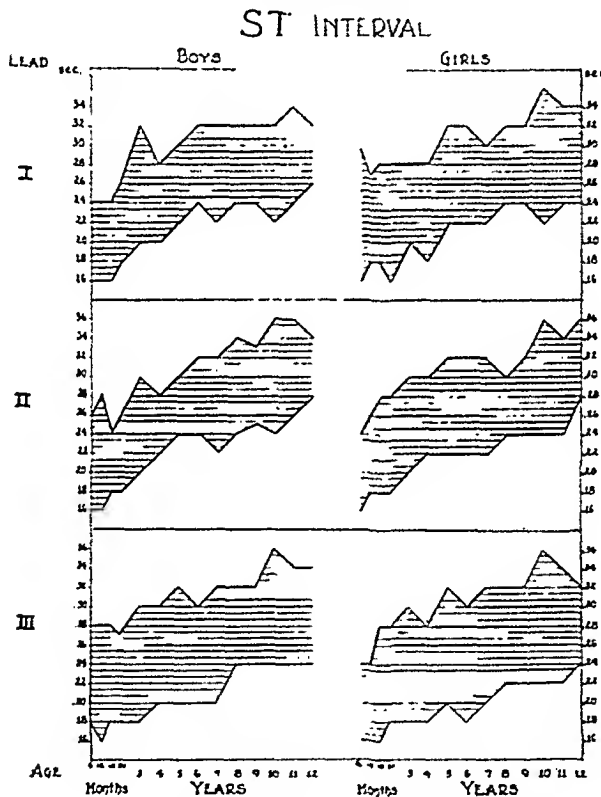


Fig. 9.—Variations in S-T intervals.

node to the Purkinje fibers appeared shortened throughout early and late childhood, but the duration of systole was markedly lengthened as age progressed.

Seham⁶ gave an average of 0.213 second for the duration of this interval from one to five years of age while our average was 0.24 second from three weeks to eight years.

Summary.—A definite lengthening with age was observed in the S-T interval.

In Table II the minimum, maximum, and average intervals observed in our series are presented.

HEART RATE

It is an accepted fact that a child's heart beats more slowly as he grows older. Lincoln and Nicolson⁸ in their series showed that the girls had a more rapid heart rate than boys up to the age of seven years. Our series showed that the girls' heart rates were more rapid from the first month to the fifth year when the boys' rates were more rapid.

TABLE II

MINIMUM, MAXIMUM, AND AVERAGE OF THE P-R, Q-S, AND S-T INTERVALS

AGE	LEADS	P-R		Q-S		S-T	
		RANGE MIN. MAX.	AV.	RANGE MIN. MAX.	AV.	RANGE MIN. MAX.	AV.
3 wk. to 6 mo.	I	0.08 - 0.14	0.107	0.04 - 0.08	0.048	0.16 - 0.30	0.203
	II	0.08 - 0.16	0.11	0.04 - 0.08	0.048	0.16 - 0.26	0.207
	III	0.08 - 0.14	0.109	0.04 - 0.08	0.05	0.16 - 0.24	0.199
7 mo. to 12 mo.	I	0.08 - 0.16	0.114	0.04 - 0.08	0.052	0.16 - 0.27	0.207
	II	0.08 - 0.16	0.12	0.04 - 0.08	0.052	0.16 - 0.28	0.214
	III	0.08 - 0.16	0.114	0.04 - 0.08	0.055	0.16 - 0.28	0.208
13 mo. to 18 mo.	I	0.08 - 0.18	0.118	0.04 - 0.08	0.056	0.16 - 0.28	0.219
	II	0.08 - 0.18	0.119	0.04 - 0.08	0.056	0.18 - 0.28	0.219
	III	0.08 - 0.18	0.116	0.04 - 0.10	0.05	0.16 - 0.28	0.216
19 mo. to 24 mo.	I	0.08 - 0.16	0.119	0.04 - 0.08	0.054	0.16 - 0.28	0.226
	II	0.08 - 0.16	0.123	0.04 - 0.08	0.053	0.18 - 0.28	0.23
	III	0.08 - 0.16	0.117	0.04 - 0.08	0.052	0.18 - 0.28	0.224
Third year	I	0.10 - 0.16	0.128	0.04 - 0.08	0.052	0.20 - 0.28	0.238
	II	0.10 - 0.17	0.13	0.04 - 0.08	0.052	0.20 - 0.30	0.243
	III	0.10 - 0.16	0.12	0.04 - 0.08	0.052	0.18 - 0.30	0.246
Fourth year	I	0.12 - 0.16	0.13	0.04 - 0.09	0.053	0.18 - 0.28	0.256
	II	0.11 - 0.16	0.13	0.04 - 0.09	0.05	0.22 - 0.30	0.25
	III	0.08 - 0.16	0.126	0.04 - 0.08	0.054	0.18 - 0.30	0.248
Fifth year	I	0.10 - 0.16	0.135	0.04 - 0.08	0.054	0.22 - 0.32	0.257
	II	0.12 - 0.16	0.135	0.04 - 0.08	0.054	0.22 - 0.32	0.26
	III	0.10 - 0.17	0.131	0.04 - 0.08	0.056	0.20 - 0.32	0.251
Sixth year	I	0.10 - 0.16	0.14	0.04 - 0.09	0.057	0.22 - 0.32	0.264
	II	0.10 - 0.16	0.139	0.04 - 0.08	0.058	0.22 - 0.32	0.267
	III	0.10 - 0.16	0.132	0.04 - 0.08	0.06	0.20 - 0.30	0.255
Seventh year	I	0.10 - 0.16	0.143	0.04 - 0.10	0.057	0.22 - 0.32	0.264
	II	0.10 - 0.17	0.138	0.04 - 0.08	0.06	0.22 - 0.32	0.268
	III	0.10 - 0.16	0.132	0.04 - 0.09	0.062	0.20 - 0.32	0.261
Eighth year	I	0.12 - 0.16	0.142	0.04 - 0.08	0.058	0.24 - 0.32	0.273
	II	0.10 - 0.16	0.142	0.04 - 0.09	0.064	0.24 - 0.34	0.274
	III	0.10 - 0.16	0.139	0.04 - 0.10	0.064	0.22 - 0.32	0.271

In checking with the physical examination, the heart rate was usually slower when calculated from the electrocardiogram than from physical examinations. The above mentioned authors found the opposite to be true, attributing the cause to some fear of the procedure of making a cardiogram. From seven months until two years of age, when the children are most difficult to handle, the heart rate was a little more rapid than during physical examination, but after they had overcome their fears the heart rate remained slower. At the fifth year the low rate was 68 in girls, and this decreased to 58 the last

four years (nine to twelve years, inclusive). The record which showed the heart rate of 58 was that of a girl whose first record at seven years four months showed a rate of 64. The most rapid heart rate of 195 was in a girl three months old. The rate of her succeeding records decreased to 88 at three years three months.

As a means of determining to what the decrease in the heart rate is due, whether prolonged contraction solely or prolonged contraction and diastole, we noted the most rapid, moderate, and slowest heart rates in boys and girls in eight age groups. We found that the increase in diastole or T-P interval was responsible for the slower rate. The time of diastole did not change more than 0.04 second up to six years while a variation of 0.10 second was observed in the eleventh year.

Summary.—The decrease of the heart rate with age paralleled the increase in diastole as shown by the T-P interval.

Table III presents the slowest, most rapid, and average heart rates observed in our age groups.

TABLE III
THE SLOWEST, MOST RAPID, AND AVERAGE HEART RATES

HEART RATE	3 WK. TO 6 MO.	7 MO. TO 12 MO.	13 MO. TO 18 MO.	19 MO. TO 24 MO.	3RD YEAR	4TH YEAR	5TH YEAR	6TH YEAR	7TH YEAR	8TH YEAR
Slowest	115	92	90	82	65	80	68	69	62	64
Most rapid	195	190	178	171	166	145	138	111	105	118
Average	142.7	141.3	123.7	116.1	107.9	101.1	95.7	89.7	88.6	83.7

SINUS ARRHYTHMIAS

Previous reports^{6, 8} show that sinus arrhythmias are found more frequently in older children. Krumbhaar⁵ considered a record to show sinus arrhythmia when the difference between the shortest and longest heart cycle was 0.10 second or more.

Accepting Krumbhaar's criterion, as the other workers have, we found 279 records, or 21.8 per cent, showing as much variation as this. The earliest evidence of sinus arrhythmia was seen in a boy and in a girl fourteen months of age. From that age on there was a constant increase in the frequency of incidence until the maximum percentage was reached in the tenth and eleventh years. This suggests that this is the period of childhood in which vagus activity becomes fully developed, since it is generally accepted that this type of activity is due to a varying degree of vagus control.

Summary.—Two hundred and seventy-nine, or 21.8 per cent, of our records showed sinus arrhythmia, the greatest incidence being in the tenth and eleventh years.

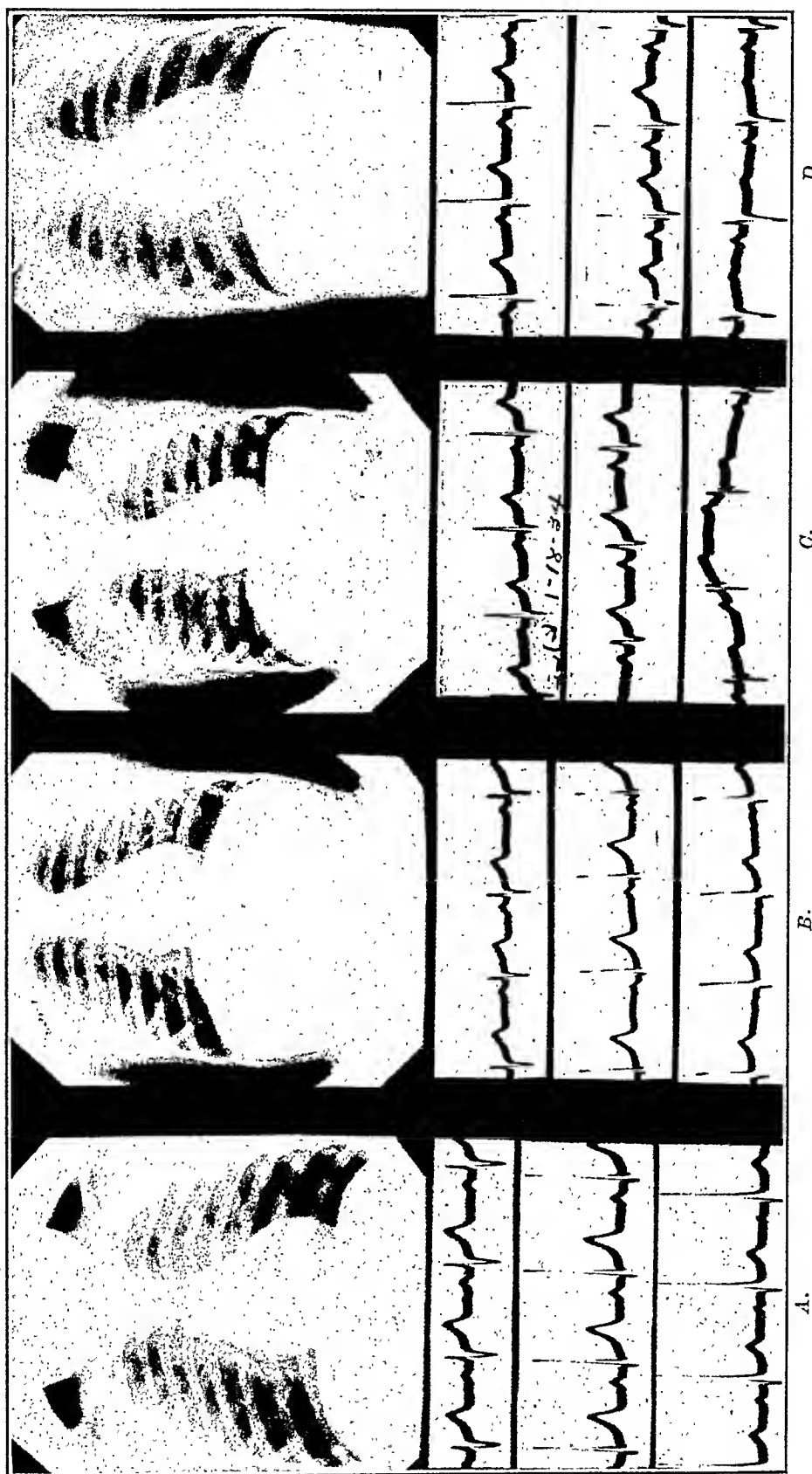


Fig. 10.—Electrocardiograms and heart roentgenograms on four children. The electrocardiograms show:
A, a right axis deviation on a boy aged seven years six months.
B, a suggestion of right axis deviation on a four-year-old girl.
C, left axis deviation on a girl three years three months of age.
D, a suggestion of left axis deviation on a boy aged five years seven months.
 Note that none of the chest roentgenograms indicates preponderance of either ventricle.

AXIS DEVIATION

The term "right axis deviation" as defined by the Heart Committee¹⁰ includes those electrocardiograms in which the main deflection of the QRS group in Lead I is downward and R_3 is larger than R_2 (Fig. 10 A). A number of earlier workers^{1, 2, 5, 6} have noted a deep S, or stressed the frequency of "right preponderance" in the first few months. In our series of records 58, or 4.5 per cent, were included under this term. Those records with a deep S_1 , but R_2 and R_3 balancing, are considered as suggestive of right axis deviation (Fig. 10 B). Sixty, or 4.7 per cent, of our cases may be so included.

Table IV shows the age occurrence of right axis deviation in the first six months.

TABLE IV

AGE	BOYS			GIRLS		
	NO. OF CASES	RT. AXIS DEV.	SUGG. RT. AXIS DEV.	NO. OF CASES	RT. AXIS DEV.	SUGG. RT. AXIS DEV.
1 to 3 mo.	58	12	9	63	16	6
4 to 6 mo.	29	2	1	28	2	3

The term "left axis deviation" may be applied to those records in which the main deflection in Lead III is downward and R_1 is larger than R_2 ¹⁰ (Fig. 10 C). The suggestion of this deviation includes those in which R_2 was equal to or higher than R_1 but with the main deflection in Lead III downward (Fig. 10 D). Under left axis deviation thirty-five records, or 2.7 per cent, were included, while twenty-six, or 2.03 per cent, showed a suggestion of left axis deviation.

Summary.—Right axis deviation was most marked during the first three months, with a notable decrease during the period from four to six months. Left axis deviation occasionally occurred in average healthy children.

SUMMARY

1. The P-wave showed higher and lower amplitudes than in the adult. Diphasic forms occurred in Leads II and III and notched forms in all leads.

2. Q-waves were deeper in boys than in girls, and there was a more gradual decrease with age in girls than in boys.

3. R-waves may be higher or lower than usual adult standards indicate. R-waves showed slurring in 457, or 35.8 per cent of the records, and notching in 56, or 4.38 per cent. R_3 alone presented M and W forms and inversion. It is difficult to classify portions of the QRS complex.

4. S-waves decreased with age in all leads.

5. Well-defined and frequently high T-waves were observed in Leads I and II. T_3 was usually of low voltage. Inversion was seen only in T_3 . It occurred in 242, or 18.9 per cent, of the cases in this lead.

6. Transmission time was shorter in hearts of children; as seen in the P-R and Q-S intervals. The S-T interval showed a definite lengthening with age.

7. Heart rates decreased with age.

8. Sinus arrhythmia was shown in 279, or 21.8 per cent, of our records and was seen most frequently in the tenth and eleventh years.

9. The greatest number of instances of right axis deviation was found in the first three months of life, with a notable decrease in the period of from four to six months. Left axis deviation occasionally occurred in average healthy children.

10. Our study indicates that normal standards must allow a wide range of individual variations in the electrocardiograms on healthy infants and children.

11. This study indicates the need for similar statistical studies through later childhood and adult life and suggests a greater variation in the normal adult electrocardiogram than is indicated by present accepted standards.

We desire to thank Dr. O. L. Huddleston and Dr. E. Durbin for assistance given in measuring some of these records and the staff of the Child Research Council for helpful suggestions.

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MINUTE VOLUME DETERMINATIONS IN MITRAL STENOSIS DURING AURICULAR FIBRILLATION AND AFTER RESTORATION OF NORMAL RHYTHM*†

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THE rôle played by the auricle in the work of the heart has been studied for many years. There have been different approaches to the solution to this problem, but all of them lead to approximately the same conclusions. The first method of approach was that of ventricular filling curves. In 1906 Yandell Henderson¹ stated that he could get very little if any change in the filling curves of the ventricle during auricular contraction. This work has since been severely criticized by Straub² and by Gesell,³ who show definitely that the Marie tambour which Henderson used was not sensitive enough for the type of work he was doing.

In 1908 Hirshfelder⁴ did some very interesting experiments on the subject. He first made ventricular filling curves in normal dogs which showed the following characteristics (Fig. 1 is a reconstruction of these curves): At the beginning of diastole, the ventricle filled very rapidly as shown by a very steep rise in the curve. Then, as the pressure between the auricles and the ventricles became equalized, this curve tapered off, so that for a short period of time, there was practically no filling. Simultaneously with auricular contraction, the filling curve again showed a steep rise and tapered off again just as before ventricular systole. The filling produced by the auricle in these normal dogs was approximately 20 per cent of the total diastolic filling of the ventricles. Hirshfelder then produced artificial mitral stenosis in these same dogs. He did this by passing a ligature around the mitral orifice in such a way that when the ligature was drawn tight, a stenosis was produced at this valve. The filling curve then took on a slightly different form. Because of the obstruction between the auricle and the ventricle, the ventricle did not fill as rapidly as in the normal dog, and therefore the curve was not as steep nor did it rise to as great a height as it did in the normal dog. Later in diastole when the pressures in the auricle and the ventricle became more nearly equal, a period was again reached when there was very little if any filling. When auricular contraction occurred, however, a considerable amount of blood was forced into the ventricles, as shown by a very rapid rise in the ven-

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tricular filling curve which led up to ventricular systole. In these dogs with mitral stenosis, the percentage of filling produced by the auricle was approximately 25 per cent as compared to the normal value of 20 per cent. He then carried on an experiment in the same way except that he faradized the auricles, causing them to fibrillate. When this occurred, the filling curve again started out just as it had in the preparation before fibrillation took place. However, as no auricular systole took place, there was no secondary rise in the curve and the ventricle never became as completely filled as it was previously. This showed then, rather conclusively, that the auricle contributed approximately 25 per cent to the filling of the ventricle in mitral stenosis and therefore, if the ventricular rates were equal, contributed approximately 25 per cent to the minute volume.

In 1910 Straub,² using the cat as the experimental animal, made a cardiometer in which the membrane on the tambour consisted of a soap

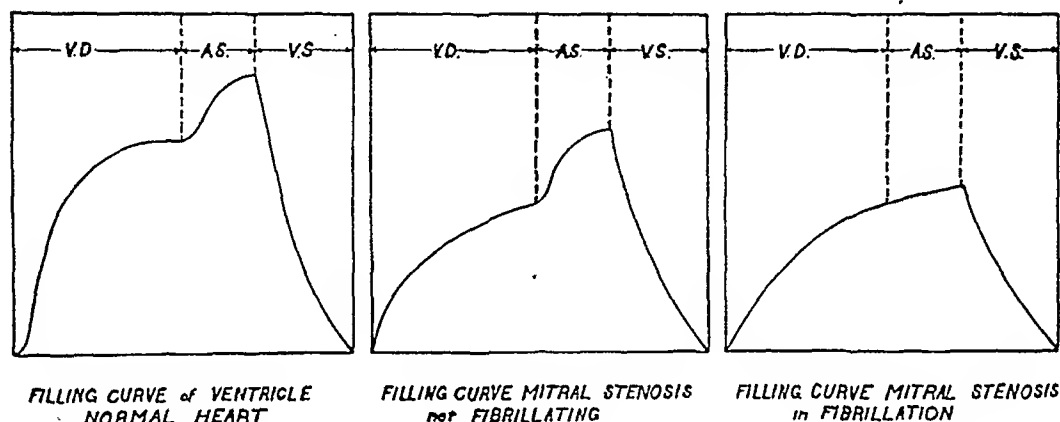


Fig. 1.—V. D., ventricular diastole; A. S., auricular systole; V. S., ventricular systole. (Reconstructed from Hirshfelder's experimental curves.)

bubble. He photographed the movements of this soap bubble on a moving film. He found that the auricle contributed some 33 to 66 per cent of the filling of the ventricle.

In 1912 DeHeer⁵ made similar ventricle filling curves and found that approximately 30 per cent of the filling of the ventricle was due to the auricle. In 1922 Wiggers and Katz,⁶ with an improved method, found that the auricles contributed from 19 to 60 per cent of the filling of the ventricle and that the average contribution of the auricle was 35 per cent.

The second method of attack was made by means of blood pressure measurements. Gesell³ in 1911 used a preparation in which he crushed the His bundle in a dog and used different rates of stimulation to the auricles and to the ventricles. He noticed definite changes in aortic pressures when different rates of stimulation of the auricle as compared with the ventricle were used. For instance, if he stimulated the auricle

thirteen times a minute and the ventricle twelve times a minute, he found that he could set up definite interference waves in the blood pressure, i.e., the maximum blood pressure occurred when the auricle contracted just before the ventricle and the minimum blood pressure curve when the auricle contracted during the ventricular systole. He also found that if the auricles were stimulated twice for each stimulation of the ventricle, the blood pressure was higher than that obtained when the auricles were stimulated at the same frequency as the ventricles. He came to the conclusion that the auricles were responsible for approximately 25 to 50 per cent of the minute volume of the heart.

The third method of approach was through minute volume determinations on animals before and during artificially produced auricular fibrillation. Lewis⁷ in 1912 used dogs and cats and found that the auricular fibrillation caused a decrease in minute volume of approximately 20 per cent. He also found that the greater the rate of the ventricle following auricular fibrillation, the greater the loss in minute volume. This is borne out also by some work by Eyster and Swarthout,⁸ using a similar method on dogs. They found that auricular fibrillation decreased the minute volume all the way from 15 to 79 per cent. In studying their tables, one finds that the 79 per cent decreases were in those dogs in which the ventricular rate became very rapid while the lower decrease in minute volume was in those dogs in which the rate was not so rapid. The last method of approach has been the determination of minute volumes in cases of auricular fibrillation in the human. Smith, Walker, and Alt⁹ in 1930 found that, when normal rhythm was restored by the use of quinidine in patients with auricular fibrillation, the minute volume increased approximately 30 per cent.

In our work we have attempted to carry out this same method. We have limited ourselves to cases of mitral stenosis for two reasons. We chose cases of mitral stenosis because we believed that the dilatation and hypertrophy of the auricles in these cases would give us a greater difference in minute volume when the normal rhythm was restored and because it is of considerable importance to know whether the use of quinidine in mitral stenosis increases the mechanical efficiency of the heart by restoring normal auricular function. The method was carried out as follows: Patients with mitral stenosis with auricular fibrillation were either brought into the hospital or kept at rest at home. They were all given digitalis, and the ventricular rates were brought down to approximately 60 to 70 per minute. Those patients who were decompensated were allowed to compensate as far as possible under this regime. The compensation was checked by physical signs and by the use of vital capacity determinations. When no further improvement was possible under this regime, minute volume studies were begun. The minute volumes were determined by the Grollman¹⁰ acetylene gas method,

a method which has yielded very excellent results in our hands. Minute volume determinations were made upon those patients whose ventricular rates had been brought down to 60 to 70 beats per minute and who were also compensated. Duplicate determinations were made on each case, and the average of these determinations was accepted as the minute volume of the patient while the auricles were fibrillating. These patients were then kept on the maintenance dose of digitalis. They were given quinidine. When the normal rhythm was restored, quinidine was reduced to a maintenance dose which, in our hands, amounts to 9 to 15 grains a day, and minute volume determinations were again made. The average of these determinations after quinidine medication was taken as the minute volume with the auricles beating regularly. In all, we have studied seventeen females and five males (Table I). The seventeen females had an average minute volume of 2.35 liters per minute during fibrillation. Of these, seven became regular, and the average minute volume of these seven after becoming regular was three liters per minute. This increase from 2.35 to 3 liters per minute is an increase of 27 per cent. The increase in the individual cases varied from 14 to 36 per cent, and the average increase in these seven cases was 26 per cent.

TABLE I

CASE	MINUTE VOLUME FIBRILLATING (LITERS PER MINUTE)	MINUTE VOLUME REGULAR (LITERS PER MINUTE)	PER CENT INCREASE
<i>Females</i>			
M. A.	2.84		
H. B.	2.85		
I. C.	3.15	3.48	14
I. F.	1.28		
E. K.	2.60		
I. K.	2.26		
L.	2.03	2.77	36
C. L.	2.62	3.38	28
H. O.	2.67		
R.	1.95		
E. S.	2.00	2.62	31
A. S.	2.12	2.67	25
G. S.	2.38	2.90	21
M. T.	2.54	3.18	25
T.	1.74		
H. W.	2.38		
M. W.	2.55		
Average	2.35	3.00	27
<i>Males</i>			
E. B.	2.64		
G. K.	3.75		
J. O.	3.85		
A. S.	2.25		
J. S.	2.41	2.87	19
Average	2.98		
Average increase for both males and females = 25 per cent			

Grollman¹⁰ has stated that the average minute volume in females is 3.6 liters per minute. Returning now to our filling curves (Fig. 1), which we have reconstructed freely from Hirshfelder's experiments in mitral stenosis, we find that our results are in very good accord with his experiments on dogs. The normal heart with a minute volume of 3.6 liters per minute corresponds to the first curve. The hearts of Hirshfelder's experimental animals with mitral stenosis and with the auricles beating regularly have a somewhat decreased rise in the ventricular filling curve. We find the minute volumes of our patients with mitral stenosis in females averaging approximately three liters per minute or about 17 per cent less than the normal. Our cases of mitral stenosis with auricular fibrillation in females correspond to the third curve reconstructed from Hirshfelder's curves of experimentally produced mitral stenosis with auricular fibrillation. We find that the minute volume here corresponds to what one would expect from a study of those curves, namely, our figure to 2.35 liters per minute is approximately 22 per cent less than the minute volume in cases of mitral stenosis without auricular fibrillation.

The series of males has been much smaller. We have studied only five males with mitral stenosis and find that their average minute volume during fibrillation is three liters per minute, or about 25 per cent under the average for normal males as determined by Grollman. In only one of these males did the rhythm become regular, and his increase in minute volume was 19 per cent on becoming regular. Because of the small number of males, it is unjustifiable in this series to draw any conclusions from average values. However, it is very probable that if the series of males were as large as the series of females, the results would be the same.

Kohn and Levine¹¹ in a recent publication have stated the belief that the restoration of normal rhythm in auricular fibrillation does not increase cardiac efficiency. In view of our results, it is difficult for us to concur in this belief. We believe that these results prove definitely that at least in mitral stenosis the restoration of normal rhythm in auricular fibrillation is of definite value in increasing cardiac efficiency.

CONCLUSIONS

1. Results show that the minute volume in mitral stenosis is frequently definitely reduced.

2. The appearance of auricular fibrillation further reduces the minute volume in mitral stenosis by approximately 22 per cent.

3. The restoration of normal rhythm, by the use of quinidine, is of definite value in that it increases the minute volume by approximately 25 per cent. The increase in cardiac efficiency justifies the use of quinidine.

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TRANSIENT COMPLETE BUNDLE-BRANCH BLOCK

REPORT OF SIX CASES

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ELECTROCARDIOGRAMS exhibiting bundle-branch block are no longer of uncommon occurrence, but this condition is usually associated with advanced heart disease and, once established, is prone to persist for the remainder of the patient's life. Transient bundle-branch block occurs relatively infrequently, and a comparatively small number of such instances have been reported in the American literature. Wolff, Parkinson, and White¹ observed eleven cases of transient bundle-branch block in apparently healthy young people. Willius and Anderson² reported a case of transient, recurrent complete bundle-branch block, unique in certain respects, and were fortunate enough to have recorded the transition from the normal to the abnormal mechanism. They called attention to the infrequency with which bundle-branch block has been reported as a transient finding and in reviewing the literature mentioned three cases of transient incomplete bundle-branch block reported by Willius and Keith³ in 1927, one case of transient complete bundle-branch block reported by Baker⁴ in 1930, and two cases of a similar nature reported by Morris and McGuire⁵ in 1932. This makes a total of seven cases in which there was a background of organic heart disease, and eleven cases in which no heart disease could be demonstrated.

In the course of the last year and a half transient bundle-branch block has been observed in five patients on the wards of the Wisconsin General Hospital and in one patient at the Madison General Hospital. Advanced heart disease was present in every instance, and in one case the finding followed a coronary thrombosis. These six cases form the basis of the present report.

CASE 1.—H. M., a man aged seventy-three years, was admitted to the Wisconsin General Hospital, Jan. 13, 1933, for treatment of bilateral senile cataracts. There were no symptoms referable to the heart except for moderate shortness of breath on exertion.

Physical examination revealed a well-developed and nourished white elderly male. The radial arteries were moderately thickened, and the pulse was slightly irregular. The blood pressure was 130 systolic and 74 diastolic. The heart was moderately enlarged to the left. The sounds were of poor quality at all areas, and no murmurs were heard. A few moist râles were noted at both lung bases posteriorly.

The blood Wassermann reaction was negative. An electrocardiogram taken Jan. 18 (Fig. 1A) showed a left bundle-branch block, as well as other disturbances of the conduction mechanism. The P-R interval varied from 0.10 to 0.29 of a second, and the QRS interval averaged 0.15 of a second.

A diagnosis was made of immature bilateral senile cataracts, coronary heart disease with moderate cardiac enlargement, advanced myocardial degeneration, and left bundle-branch block. The patient was discharged Jan. 20, 1933, and instructed to return in three months for further observation and possible operation.

The patient was readmitted to the hospital April 25, 1933, having received no medical treatment in the interim. The physical examination was essentially the same as on the previous admission, but the electrocardiogram taken May 2, 1933 (Fig. 1*B*), showed a left axis deviation but no evidence of bundle-branch block. The P-R interval was 0.21 and the QRS 0.10 of a second. On May 3, 1933, a preliminary iridectomy was successfully performed on the right eye. Recovery was uneventful, and the patient was discharged May 10.

CASE 2.—Mrs. M. L., a woman of sixty-one years, was admitted to the Wisconsin General Hospital Nov. 27, 1933, with a chief complaint of shortness of breath which

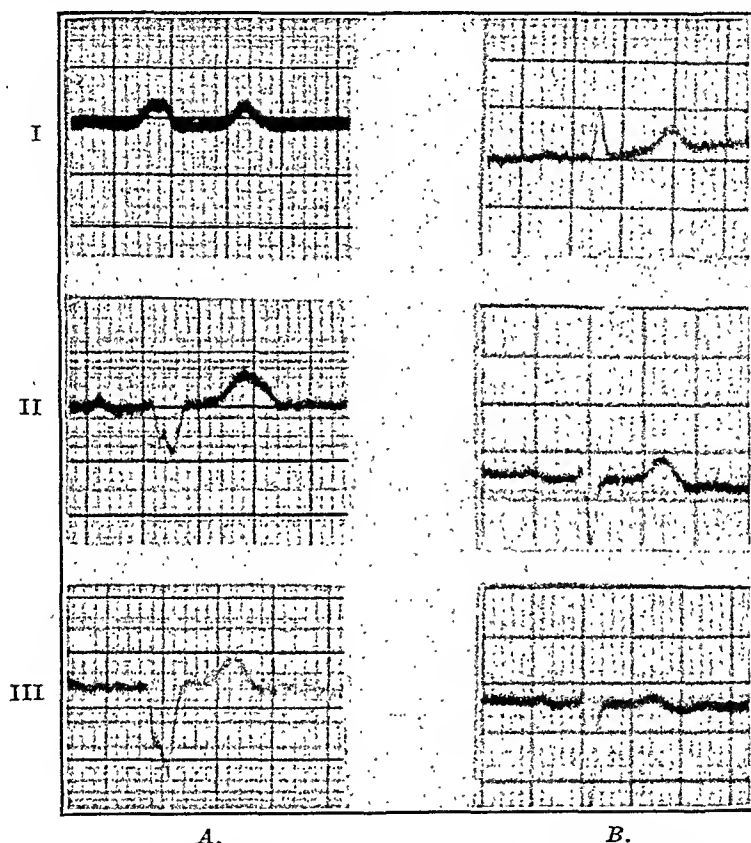


Fig. 1.—(Case 1.) Male, aged seventy-three years. *A*, electrocardiogram taken Jan. 18, 1933, showing left bundle-branch block. *B*, tracing taken May 2, 1933, showing left axis deviation but no bundle-branch block.

had been present for the preceding four years. She was known to have had an elevated blood pressure for several years. Five days before admission she became very ill with an attack of severe epigastric distress accompanied by marked shortness of breath and agonizing pain over the heart radiating to both sides of the neck. This attack lasted nearly twenty-four hours in spite of repeated hypodermic injections of morphine.

Physical examination revealed a well-developed and nourished woman of 61, obviously seriously ill. The skin was slightly cyanotic, and dyspnea was marked. The retinal arteries showed marked sclerosis, and the veins were definitely engorged. The radial arteries were moderately thickened; the pulse was reduced in volume and was regular at a rate of 50. The blood pressure was 155 systolic and 85 diastolic. The heart was moderately enlarged to the left, and the heart sounds were distant

and of poor quality. No friction rub could be detected. Fine moist râles were heard at both lung bases posteriorly, and there was moderate pitting edema of both lower extremities.

The blood Wassermann test was negative. The blood count showed 14,950 leucocytes. An electrocardiogram taken the day after admission (Fig. 2A) showed typical left bundle-branch block. There appeared to be a 2:1 A-V block in Lead I although the P-R interval was well within normal limits. In Leads II and III the P-wave occurred about midway between the QRS complexes. The QRS interval was 0.15 of a second. A diagnosis was made of coronary and hypertensive heart disease with recent coronary thrombosis, moderate cardiac enlargement, left bundle-branch block, and congestive failure, functional capacity Class III.

The patient was kept at complete bed rest and oxygen was administered per nasal catheter. One and one-half grains of aminophyllin were given three times daily by

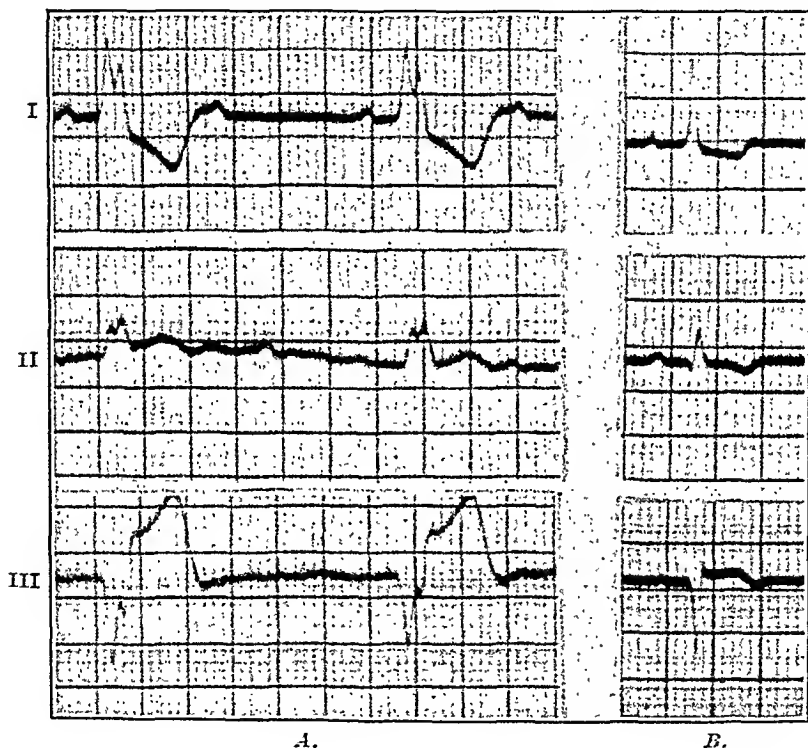


Fig. 2.—(Case 2.) Female, aged sixty-one years. A, electrocardiogram taken Nov. 28, 1933, showing typical left bundle-branch block. Coronary occlusion had occurred six days previously; 2:1 A-V block appears in the first lead. In Leads II and III a definite P-wave seems to appear only at a point about midway between the QRS complexes. B, tracing taken Dec. 4, 1933, two weeks after the coronary occlusion. Bundle-branch block has disappeared, but the deep Q_s, the S-T segment deviation, and the T-wave inversion are evidences of coronary involvement.

mouth. An electrocardiogram taken Dec. 4, 1933 (Fig. 2B) while the patient was receiving oxygen showed a return to normal rhythm and a complete absence of the bundle-branch block. However, a very deep Q_s, definite S-T segment deviation in Leads I and III, and inverted or diphasic T-waves in all leads, were characteristic of recent infarction. The oxygen was discontinued on December 6. By Jan. 15, 1934, all signs of congestion had disappeared. A third electrocardiogram taken Jan. 16, 1934, and the fourth one, taken a few days before dismissal from the hospital, showed the progressive changes commonly found following a coronary thrombosis, but bundle-branch block was not present after the first electrocardiogram. The patient was discharged from the hospital on Feb. 10, 1934.

CASE 3.—J. E. N., a farmer, aged sixty-six years, was admitted to the Wisconsin General Hospital July 12, 1933, for repair of an inguinal hernia. For some time he had been troubled with palpitation and shortness of breath on exertion and recently had frequently been awakened at night by severe attacks of shortness of breath, necessitating his sitting up in a chair.

On physical examination the patient appeared to be a well-developed and somewhat overweight man in no apparent distress. The peripheral arteries showed slight thickening. The pulse was regular at a rate of 85 and the blood pressure was 170 systolic and 90 diastolic. The heart was moderately enlarged to the left. The heart sounds were somewhat distant, and a systolic murmur could be heard at the apex transmitted to the axilla. There was no evidence of congestive failure. The right inguinal ring was markedly enlarged, and the right side of the scrotum was filled with a large reducible mass. The blood Wassermann test was negative.

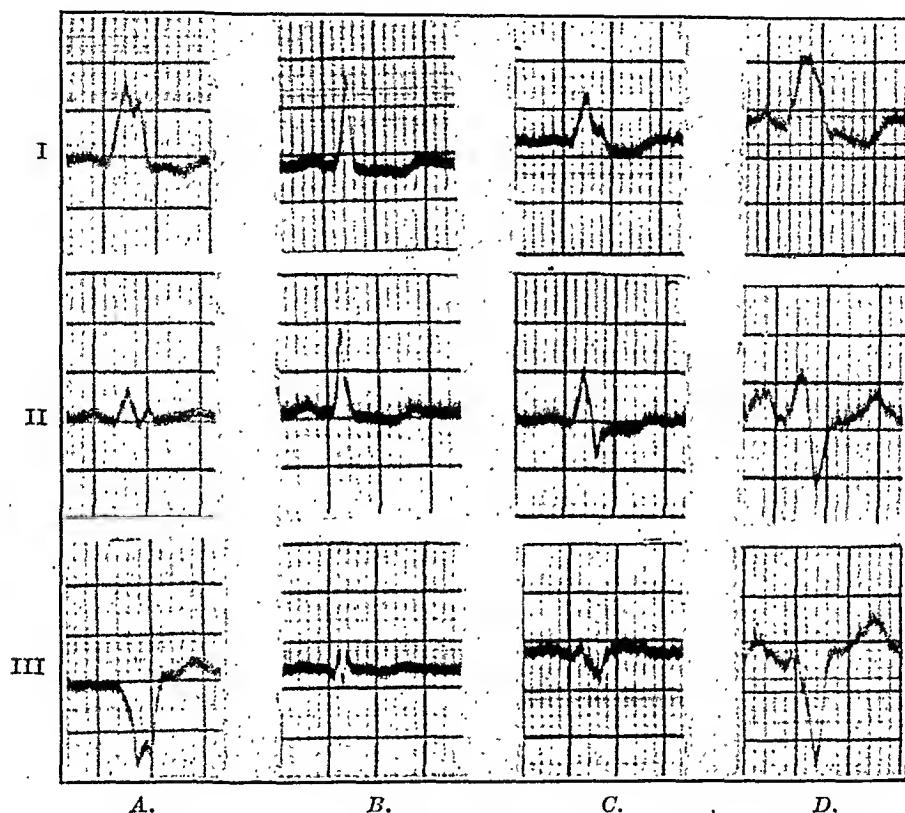


Fig. 3.—(Case 3.) Male, aged sixty-six years. *A*, electrocardiogram taken Aug. 8, 1933, showing typical left bundle-branch block. *B*, tracing taken Aug. 30, 1933, after bed rest, oxygen per nasal catheter, and complete digitalization. The bundle-branch block has entirely disappeared. *C*, electrocardiogram taken Sept. 23, 1933, three days after vasectomy had been performed. Left bundle-branch block has returned although the tracing differs in several respects from that taken on August 8. *D*, electrocardiogram taken April 20, 1934, on readmission to the hospital. Marked congestive failure present. Persistent bundle-branch block with evidences of progressive myocardial degeneration.

A diagnosis was made of right indirect inguinal hernia, coronary and hypertensive heart disease, moderate cardiac enlargement, relative mitral insufficiency, functional capacity Class IIA.

The inguinal hernia was repaired surgically July 15, 1933. On August 1 the patient complained of sharp pain in the lower left chest on deep inspiration. The skin was covered with a cold sweat, and the lips were cyanotic. A pleural friction rub could be heard over the lower left chest laterally. Both the pain and the friction rub lasted for three days. On August 6 he complained of a sharp pain in the lower right chest aggravated by inspiration. The pain was so severe on lying

down that the patient was forced to sit up all night. The respirations were shallow, rapid, and irregular. The pulse rate was 104. The skin was cool and very moist. The blood pressure was 185 systolic and 110 diastolic. Gallop rhythm was present at the apex. The liver was slightly enlarged, and there was pitting edema of both lower extremities. An electrocardiogram taken August 8 (Fig. 3A) showed a slight tachycardia and a typical left bundle-branch block. The P-R interval was 0.14 and the QRS 0.16 of a second. Oxygen was administered by nasal catheter and digitalization was started. The patient gradually improved, and on August 30 another electrocardiogram (Fig. 3B) was taken which showed no evidence of bundle-branch block although there were still definite signs of advanced myocardial changes. The S-T segments were depressed in Leads I and II, and the T-waves were diphasic in all leads. The P-R interval was 0.16 and the QRS 0.09 of a second.

A few days later the patient developed an epididymitis and was transferred to the genitourinary service for treatment. On Sept. 20, 1933, a left vasectomy was performed. Three days later the electrocardiogram was repeated (Fig. 3C) and showed a return of the bundle-branch block and decreased amplitude of the QRS complexes. The P-R interval was 0.13 and the QRS 0.14 of a second. He improved steadily and was discharged on Nov. 28, 1933.

On April 18, 1934, the patient was readmitted to the hospital complaining of weakness, shortness of breath, loss of appetite, and pain over the lower part of the abdomen. He frequently became so short of breath at night that he had to get up and sit in a chair. He had gained 35 pounds in weight during the preceding four months.

Physical examination revealed marked dyspnea and cyanosis, marked cardiac enlargement, and general anasarca. The electrocardiogram taken April 20, 1934 (Fig. 3D), showed a left bundle-branch block. The rhythm was regular at a rate of 100. The QRS complexes were somewhat changed in shape and amplitude as compared with the previous tracing (Fig. 3C), and the intraventricular conduction time was considerably lengthened. The P-R interval was 0.16 and the QRS 0.18 of a second. The patient was kept at complete rest, digitalized, and the fluid intake limited to 1,500 c.c. per day. He improved on this regime and was discharged on May 1, 1934.

CASE 4.—N. P., a farmer, aged sixty-five years, was admitted to the Wisconsin General Hospital Dec. 28, 1933, complaining of shortness of breath. He had felt fairly well and had been able to do his farm work until August 29, when he had a sudden attack of "indigestion" accompanied by loss of taste and marked dryness of the mouth. On recovery from this attack he noticed that he was very short of breath, particularly on exertion. He coughed a great deal, especially in the morning, and raised large amounts of sputum. Both the cough and the shortness of breath had become gradually worse until just before his admission to the hospital, when he was able to do only a few minor chores on the farm. There had been a loss of 20 pounds of weight during the past four years. The family history was significant in that both parents had died of heart disease.

Physical examination revealed a rather small, elderly man, who had obviously been losing weight. Ophthalmoscopic examination revealed moderate sclerosis of the retinal arteries and definite engorgement of the retinal veins. The radial and brachial arteries were markedly sclerotic. The blood pressure was 170 systolic and 100 diastolic. There was slight enlargement of the heart to the left. The heart sounds were distant, and no murmurs were heard. Many crepitant, wheezing and sibilant râles were heard throughout both lungs, more marked at the bases. The liver edge was palpable 2 cm. below the right costal margin.

The blood Wassermann test was negative, and the sputum was repeatedly negative for tubercle bacilli. Lipiodol insufflation of the lungs showed definite bronchiectatic

dilatation in both lower lobes. An electrocardiogram taken Jan. 2, 1934, showed a normal sinus rhythm at a rate of 85 with one ventricular premature contraction following each normal beat. The QRS complexes were of low voltage in all leads and slightly slurred in Leads I and III. The P-R interval was 0.16 and the QRS 0.09 of a second. This tracing was interpreted as consistent with rather advanced degenerative changes in the myocardium, but indicated no extensive interference with the conduction mechanism.

A diagnosis was made of bronchiectasis, emphysema, coronary and hypertensive heart disease with slight cardiac enlargement, myocardial degeneration, dilatation of the aorta, extrasystolic arrhythmia, and lowered cardiac reserve, Class IIA. He was discharged from the hospital Feb. 3, 1934.

On Nov. 16, 1934, the patient was readmitted complaining of progressive weakness and increasing shortness of breath. Recently he had noted swelling of the ankles when up and around. The cough had persisted.

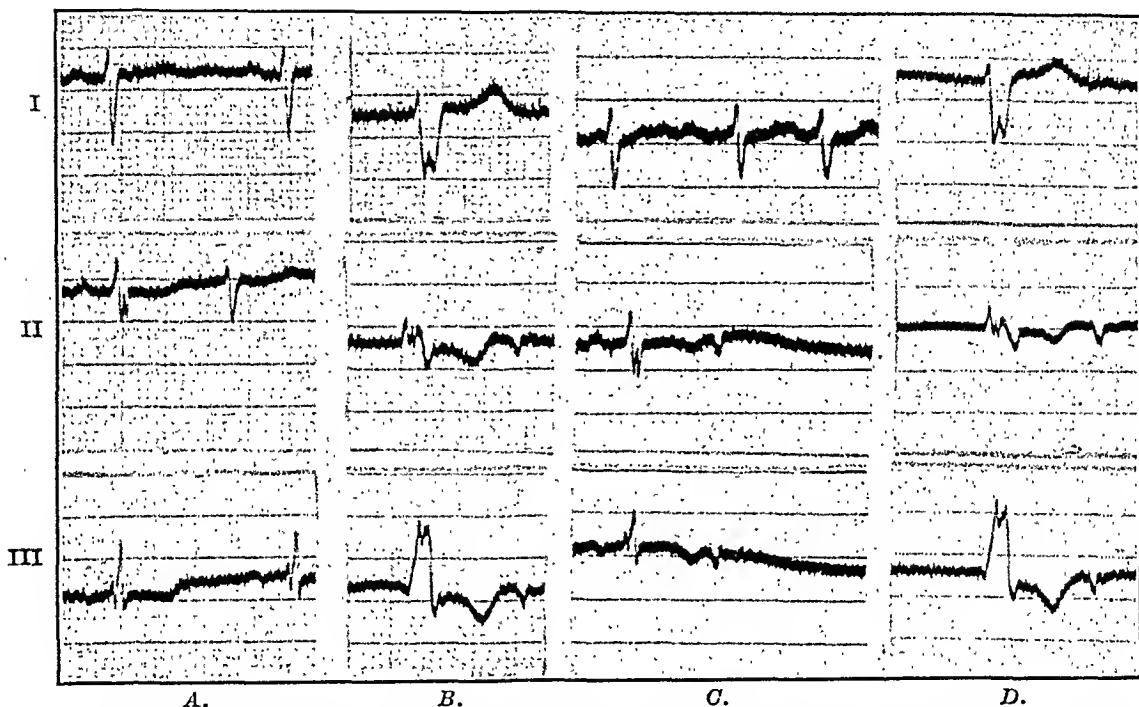


Fig. 4.—(Case 4.) Male, aged sixty-five years. A, taken Nov. 26, 1934. Normal rhythm is interrupted by periods of bigeminal rhythm, the second beat of the couplet apparently being an ectopic beat arising close to the A-V node. Right axis deviation but no evidence of bundle-branch block. B, taken Dec. 12, 1934, showing typical right bundle-branch block. Patient at bed rest and receiving maintenance dose of thevetin. Note inverted P-wave following the T-wave in Leads II and III. C, taken Dec. 17, 1934. No change in treatment. Lead I shows paroxysmal auricular fibrillation. Bundle-branch block has disappeared. D, taken Dec. 29, 1934, when patient was obviously failing. Right bundle-branch block has recurred.

On physical examination he was obviously dyspneic, and the lips and fingers were cyanotic. The blood pressure was 128 systolic and 100 diastolic. A positive centrifugal venous pulse was present. The heart sounds were distant, and no murmurs were heard. Frequent extrasystoles were noted on auscultation. The liver was palpable 4 cm. below the right costal margin. Numerous moist râles were heard throughout both lungs. Moderate pitting edema was present in the lower extremities. The diagnosis was the same as on the first admission except that the heart disease had become the primary factor, and the functional capacity was regarded as Class III.

The patient was put at complete bed rest and treated for congestive failure, oxygen being administered continuously by nasal catheter. An electrocardiogram

taken November 19 (Fig. 6A) showed in Lead I an apparently normal sinus mechanism with right axis deviation changing to a right bundle-branch block and at the same time a shift of the pacemaker to a point in the neighborhood of the A-V node. The onset of the bundle-branch block was preceded by a QRS complex apparently of a transitional type. One week later, on November 26, the electrocardiogram (Fig. 4A) showed periods of normal rhythm alternating with periods in which each normal beat was followed by a premature contraction apparently arising close to the A-V node. There was right axis deviation but no evidence of block. The P-R interval was 0.17 and the QRS 0.09 of a second. Oxygen was discontinued on December 1, and the next electrocardiogram, taken December 12 (Fig. 4B), showed a typical right bundle-branch block and a regular rhythm in which the pacemaker was situated in or below the A-V node as the P-waves were inverted and followed closely after the T-waves. The QRS interval was 0.16 of a second. For a short time the general condition appeared to improve slightly from day to day and on December 17 the electrocardiogram (Fig. 4C) showed an absence of the bundle-branch block. A short paroxysm of auricular fibrillation was recorded in the first lead but in Leads II and III there was a definite bradycardia and a blocked ectopic auricular rhythm which had been noted on a previous occasion. The P-R interval was 0.17 and the QRS 0.10 of a second. A few days later, the family, who were aware of the poor prognosis, expressed the desire to have the patient return home, and on December 21 an attempt was made to get him dressed for the trip, but the exertion produced such marked dyspnea that the idea had to be abandoned. The patient lost ground steadily, and on December 26 he complained of a severe pain over the precordium which lasted for several hours. On the following day a pleuro-pericardial friction rub was noted close to the left cardiac border. An electrocardiogram taken December 29 (Fig. 4D) showed a return of the right bundle-branch block, and the same rhythm as noted on December 17 (Fig. 4C). From this point on the clinical course was progressively downhill and the patient expired Jan. 5, 1935.

Necropsy was performed six hours post mortem and the most important findings were in the lungs and heart. The lungs showed marked emphysema and a congenital type of bronchiectasis. The heart weighed 430 gm. The left coronary artery was somewhat tortuous, with a small amount of thickening and slight longitudinal furrowing. The myocardium was rather pale with small areas of raised scarring. The aortic cusp of the mitral valve was thickened and contained a small area of calcification. Microscopic examination of the myocardium showed hypertrophy, marked diffuse fibrosis, some lipomatosis, moderate vacuolization and hyaline degeneration of the muscle fibers. The lungs, liver, spleen, and kidneys all showed marked chronic passive congestion.

CASE 5.—Mrs. J. B., aged fifty-six years, was admitted to the Wisconsin General Hospital, March 13, 1931, with a chief complaint of pain in the abdomen. There had been no symptoms referable to the heart. The past history included rheumatic fever, several attacks of pleurisy, and cholecystectomy in 1929.

On physical examination the pulse was regular at a rate of 90. The blood pressure was 128 systolic and 92 diastolic. The peripheral arteries were slightly sclerotic. The heart was slightly enlarged to the left. The heart sounds were normal at all areas; no murmurs were heard; and there were no signs of congestive failure. A diagnosis was made of peptic ulcer and postoperative abdominal adhesions.

The day following admission the patient experienced an attack of severe vomiting, the vomitus containing a small amount of blood. She was placed on routine treatment for acute gastric ulcer and gradually improved. On April 10, 1931, she ex-

perienced a second attack accompanied by upper abdominal pain of such severity as to be controlled with difficulty by morphine. Gradual improvement followed this attack and on April 15 an electrocardiogram (Fig. 5A) showed normal rhythm, rate 100, left axis deviation, S_1 and S_2 widened and slurred. The S-T segment was slightly depressed in Leads I and II, with upward convexity in Lead II but practically isoelectric in Lead III. T_2 was slightly inverted and T_3 was sharply inverted. The P-R interval was 0.16 sec., and the QRS 0.14 sec. Because of the electrocardiographic findings it was felt that the recent attack might have been of coronary origin. An electrocardiogram taken May 22, 1931 (Fig. 5B), showed an upright T_2 and T_3 with the P-R and QRS intervals within normal limits. The patient was discharged May 26, 1931, very much improved.

On Feb. 27, 1934, the patient was readmitted for a pelvic operation. At this time she complained of some dyspnea on exertion. The physical examination was

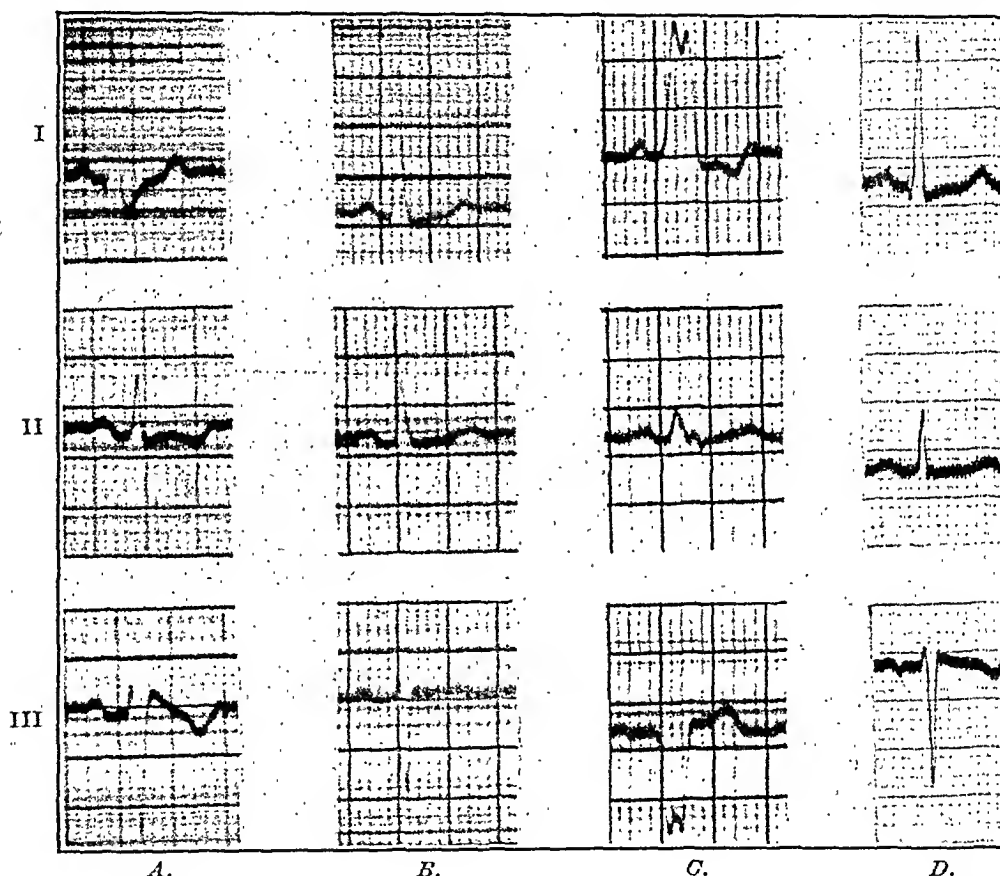


Fig. 5.—(Case 5.) Female, aged fifty-six years. A, electrocardiogram taken April 15, 1931, five days after an attack which may have been a coronary occlusion. No evidence of bundle-branch block. B, electrocardiogram taken May 22, 1931. Changes in T_2 and T_3 consistent with previous coronary occlusion. C, electrocardiogram taken March 1, 1934, showing definite left bundle-branch block. D, electrocardiogram taken Jan. 18, 1935. Bundle-branch block has disappeared.

essentially the same except that the blood pressure was found to be 180 systolic and 100 diastolic. A diagnosis was made of rheumatic and hypertensive heart disease, slight cardiac enlargement, functional capacity, Class IIA. An electrocardiogram taken March 1, 1934 (Fig. 5C), showed a definite left bundle-branch block. An operation for perineal repair was performed March 5, 1934, and the patient made an uneventful recovery, being discharged from the hospital March 30, 1934.

The patient was admitted for the third time Jan. 4, 1935, for the treatment of a ventral hernia which had developed in the wound of an old abdominal incision. The physical examination was essentially the same as on the previous admissions.

The blood pressure was 170 systolic and 108 diastolic. An electrocardiogram taken Jan. 18, 1935 (Fig. 5D) showed the bundle-branch block to have disappeared although the S-T segment still showed slight deviation in Leads I and III. The patient was fitted with a belt for the support of the ventral hernia and discharged Jan. 24, 1935.

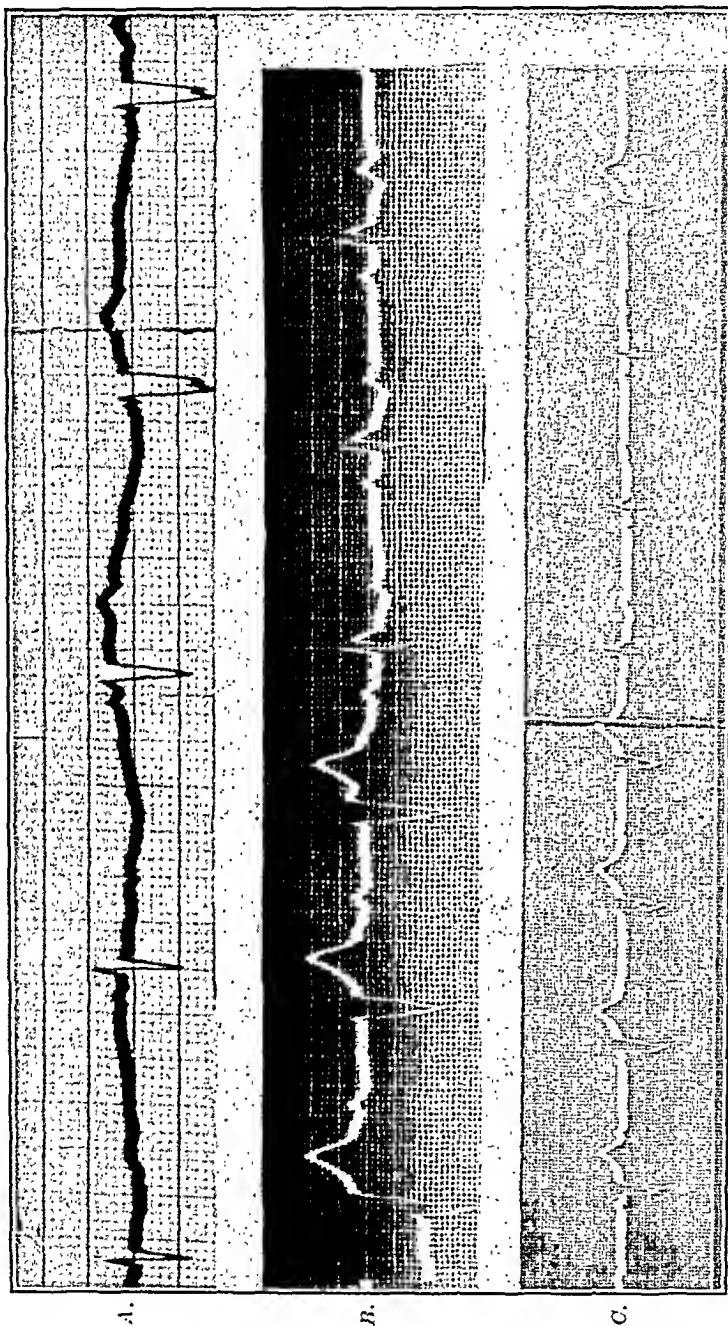


FIG. 6.—Three instances of transition to and from bundle-branch block. A, Case 4, Lead I taken Nov. 19, 1934. B, Case 6, female aged fifty-four years, coronary sclerosis, Lead III taken June 12, 1935. C, Case 6, Lead III taken June 14, 1935.

*CASE 6.—Mrs. D. R., a woman aged fifty-four years, was admitted to the Madison General Hospital on June 11, 1935, with a chief complaint of shortness of breath. The patient stated that for the past four years she had had attacks of what she termed "asthma" which had been increasing in frequency and severity

*Case included with the kind permission of Dr. J. S. Supernaw, Madison, Wis.

recently. She was unable to lie down during the attacks, and they were usually followed by a period of weakness lasting for one or more days. Except for occasional palpitation she had no other symptoms referable to the heart although she had been known to have "heart trouble" for several years. The past history included a tumor of the right breast with radical amputation six years previously and a removal of a tumor from the right axilla two years later. Cholecystectomy and appendectomy had been performed some years before.

On physical examination the pulse was found to be regular at a rate of 54, and the blood pressure was 238 systolic and 104 diastolic. Marked dyspnea was present. The right breast had been removed. The heart was enlarged to the left, and there was a systolic murmur at the apex, transmitted to the axilla. A systolic murmur was audible also at the aortic area. The lungs were clear, and there was no edema of the extremities.

An electrocardiogram taken on June 12 (Fig. 6B) showed complete heart-block alternating with periods of 2:1 A-V block, the antricular rate varying between 85 and 90 and the ventricular rate between 43 and 45. Left bundle-branch block was present in Leads I and II but disappeared during the taking of Lead III, the transition having been recorded. The QRS complexes were widened and slurred in all leads, the QRS interval being 0.15 of a second. T_1 was inverted. An electrocardiogram taken June 14, 1935 (Fig. 6C), was similar to the one taken two days previously, and again a transition period was recorded in Lead III. The patient remained in the hospital under observation for six weeks, during which time it was found that the attacks responded promptly to 1/100 of a grain of nitroglycerin. Rather large doses of barbiturates and frequently repeated doses of nitroglycerin kept her fairly free from attacks of dyspnea. She was discharged very much improved Aug. 6, 1935.

DISCUSSION

All of the patients here reported were above fifty-four years of age and at a period of life when coronary disease and degenerative changes are known to be extremely prevalent. Coronary sclerosis, hypertension, or a combination of the two, was demonstrable in each instance. In Cases 1 and 5 there was no apparent change in the clinical condition between the time that the bundle-branch block was first discovered and the time it was found to have disappeared, but in the other four cases there seemed to be a definite relationship between the presence of the bundle-branch block and the condition of the circulation in general. This was most graphically illustrated in Case 2 in which the bundle-branch block was present directly following a coronary thrombosis but disappeared during the period of recovery and the establishment of collateral circulation. The period during which this patient was under observation was marked by steady and gradual improvement, and no recurrence of the bundle-branch block was noted. In Cases 3 and 4 the bundle-branch block appeared and reappeared during periods of decompensation and persisted as long as signs of circulatory failure were in evidence but disappeared when compensation was restored. When the condition of the myocardium reached a point where congestive failure could no longer be overcome, the bundle-branch block became permanent.

The explanation of the mechanism is simple, as it appears to be plainly a matter of circulation and nutrition to the conducting tissues. When the myocardium was failing and the general circulation was obviously inadequate, it was reflected in the coronary circulation by the appearance of bundle-branch block and other conduction disturbances. As the general circulation improved under treatment, the blood supply to the myocardium and conduction system became sufficient to permit the transmission of the impulse along the normal pathways. Widespread damage throughout the myocardium, as was demonstrated at necropsy in Case 4, is undoubtedly an important contributing cause, and in the presence of such a condition a temporary decrease in the efficiency of the coronary circulation is the deciding factor in the production of marked disturbances in the conduction mechanism.

It was an interesting circumstance that the one case which exhibited right bundle-branch block showed a right axis deviation in the records in which the bundle-branch block was absent, and similarly, the five cases in which there was a transient left bundle-branch block showed either a left axis or a tendency to left axis deviation in the "normal" records.

Willius and Anderson remarked that transient bundle-branch block is probably more common than the number of reported cases would indicate, and this view is supported by the occurrence of these six cases in a relatively short space of time.

SUMMARY

Six cases of transient bundle-branch block are presented, three of which show one or more recurrences. All of the patients were above fifty-four years of age and in every instance organic heart disease was demonstrable, the etiology being coronary disease, hypertension, or a combination of the two. In two of the six cases the occurrence of the bundle-branch block was closely associated with periods of myocardial failure, and in one case was present for a time following coronary occlusion. In two instances no associated change was demonstrable in the general circulatory condition. One patient died and came to necropsy, and the other five are still living.

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THE INFLUENCE OF POSTURE ON PARTIAL HEART-BLOCK*

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IT HAS long been known that there is a heightened vagus effect in the reclining position as compared to the upright. Mosso¹ in 1884 attempted to explain the phenomenon, but physiologists even today, although recognizing its existence, are uncertain as to the cause. Its application to clinical medicine theoretically would be limited to conditions where the sympathetic-parasympathetic balance is so delicately adjusted that a slight added vagus effect would determine parasympathetic predominance. A case of partial heart-block was observed in a case in which just such a situation apparently existed, and its analysis suggests that the condition may not be infrequent.

CASE REPORT

A banker, sixty-four years of age, was first seen on April 28, 1935, with the chief complaints of "dizzy spells" accompanied by occasional vomiting, of one month's duration. The family history was irrelevant, as was the past history with the exception of an abscess on the left side of the neck near the angle of the jaw three years previously. This was excised and left a rather deep scar. The present illness began with a sudden attack of dizziness which lasted off and on for several hours. It was accompanied by nausea and vomiting. Similar attacks of varying duration occurred at irregular intervals, but none so severe or prolonged as the first. There was no apparent relation to time of day or to posture as attacks appeared both while he was lying down and while he was sitting. No attacks, however, were recalled as having occurred while he was standing. Since onset some palpitation and a feeling of irregular heartbeat occurred. There was no loss of consciousness at any time. The only medication had been 0.3 c.c. of tincture of spiroanthus two days before admission.

Physical examination revealed a well-preserved man of sixty-four years. Other than a small deep scar in the neck just beneath the angle of the left mandible and a moderate amount of postural emphysema, the positive findings were limited to the cardiovascular system. The heartbeat was not visible, and there was no enlargement to percussion. The rate (patient supine) was 48, and the rhythm was grossly irregular. The sounds were faint but otherwise normal. The radial arteries and those of the eyeballs were distinctly sclerosed. Laboratory findings were negative other than a roentgen ray film of the chest, which showed a slight enlargement of the heart to the left and a widened and much lengthened aorta.

A significant fact was that on examination of the heart when the patient was standing, the rate was 96 and the rhythm became apparently regular. Then in the supine position the rate immediately returned to 48 and the rhythm was irregular. The patient was placed under the fluoroscope on a tilt-top table. When he was supine, the rate was estimated at 36. The table was slowly tilted toward the vertical position, and, when it made an angle of approximately 70 degrees with the floor, the rate suddenly doubled and remained so as long as the table was no more hori-

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zontal than this. When the table was tilted back toward its original position, the rate again slowed. This process was repeated several times, and the phenomenon was observed consistently.

Electrocardiograms taken with the patient in various positions revealed a partial heart-block. With the patient supine the auricular rate was 62, the ventricular rate 35, giving a ratio of approximately 1.8:1. The P-R interval varied from 0.2 to 0.4 second (Fig. 1). With the patient sitting erect, the auricular rate remained about the same, but the ventricular beats increased to 43 per minute, a ratio of about 1.4:1 (Fig. 2). When the patient was standing, the auricular and the ventricular rates were 71 (Fig. 3).

The effect of exercise was tested. With the patient reclining and also before stepping upon a chair several times until dyspnea was pronounced, the auricular beats were 72 and the ventricular 53. Immediately after exercise with the patient supine the auricular rate was 80 and the ventricular rate 75, with the P-R interval prolonged (Fig. 4). With the patient standing, the auricular rate promptly rose to 92, with the ventricle responding to each impulse over an observation period of one minute (Fig. 5).

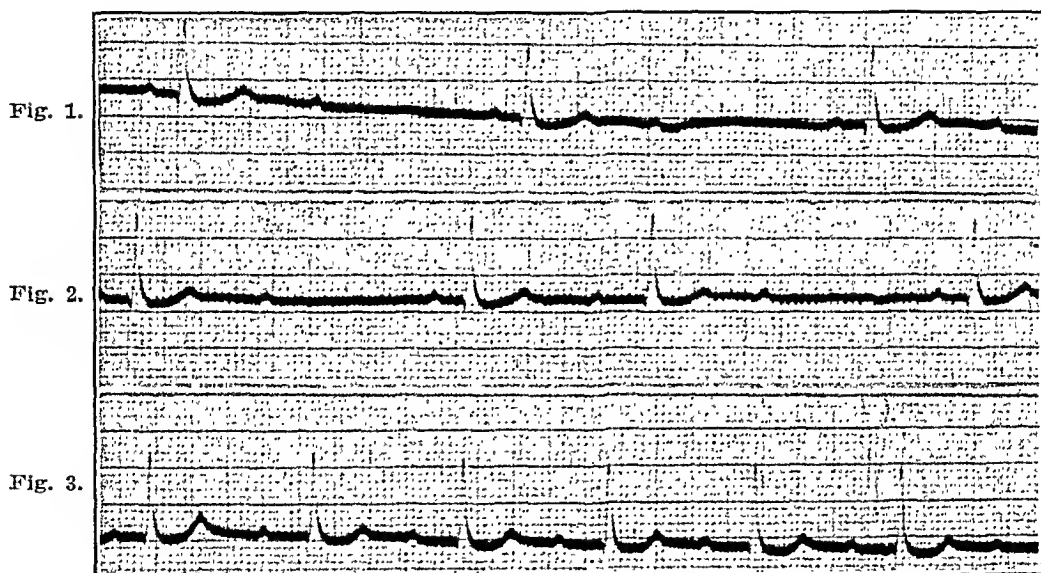


Fig. 1.—Patient supine: P-R interval, 0.2 to 0.4 sec.; auricular rate, 62; and ventricular rate, 35.5.

Fig. 2.—Patient sitting: auricular rate, 62; ventricular rate, 43; and P-R interval, 0.2 to 0.4 sec.

Fig. 3.—Patient standing: P-R interval, 0.28 sec.; auricular rate, 71; and ventricular rate, 71.

Atropine sulphate was shown to have a marked effect on the conduction mechanism. Before the administration of 0.0012 gm. subcutaneously, the auricular and the ventricular rates with the patient reclining were 60 and 45, with the P-R interval extending from 0.2 second to 0.34 second. Forty-five minutes after the administration of atropine the auricular and the ventricular rates were 80 with the patient supine, and the P-R interval became stabilized at 0.24 second (Fig. 6). The patient was then given 0.0006 gm. of atropine sulphate by mouth every eight hours. The conduction mechanism remained normal thereafter in all positions, although the P-R interval continued to be somewhat prolonged. This dose of atropine was continued after discharge from the hospital, with occasional omissions of one dose on days when dryness of the throat became excessive. No further symptoms occurred. On June 22, while the patient was still taking atropine, there was no abnormal alteration in rate with change of posture. The P-R interval was 0.22 second (Fig. 7).

DISCUSSION

When the vagus influence on the heart rate in the case here reported was first recognized, it was considered probable that there was mechanical pressure somewhere about the carotid sinus or vagus trunks. The symptoms in this case were not unlike those reported by Weiss² in patients in whom such mechanical factors had been discovered. This supposition seemed all the more probable because of the scar in the neck quite near the carotid sinus. However, digital pressure over that area as well as on the right side of the neck caused no pronounced slowing of the rate, regardless of the patient's position. The mediastinum, examined

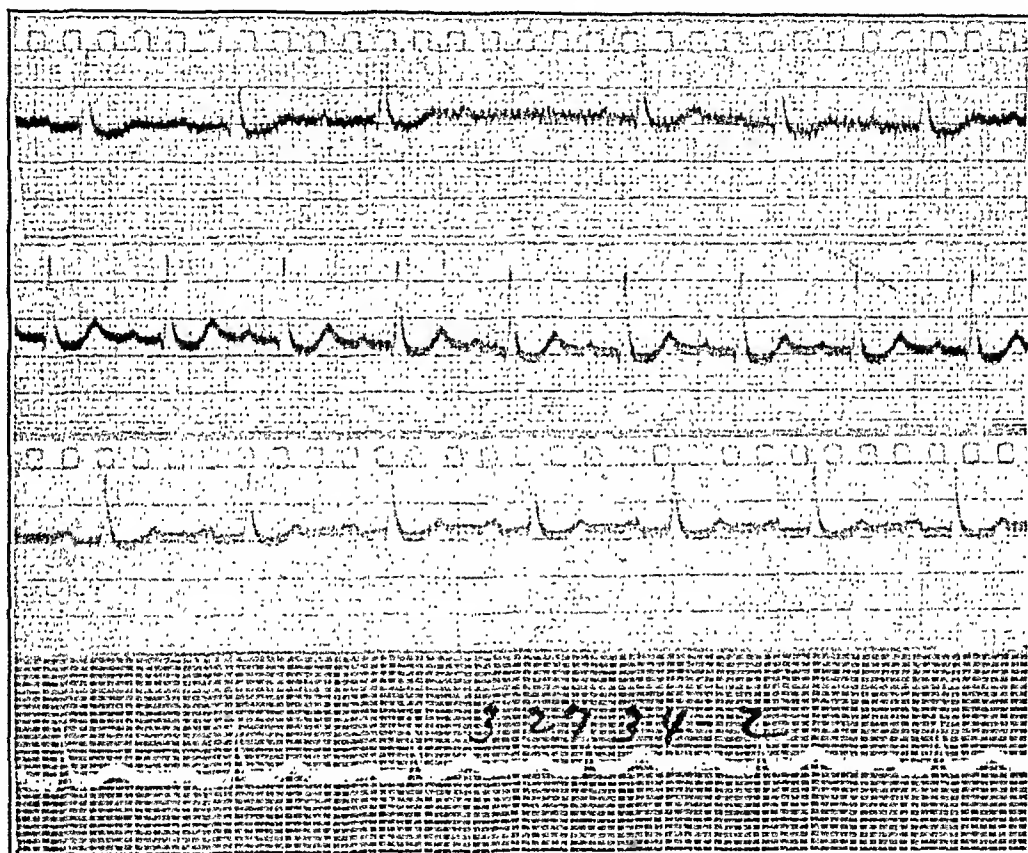


Fig. 4.—Patient supine after exercise: auricular rate, 80; ventricular rate, 75; and P-R interval, 0.22 to 0.32 sec.

Fig. 5.—Patient standing after exercise: auricular rate, 92; ventricular rate, 92; and P-R interval, 0.2 sec.

Fig. 6.—Patient supine forty-five minutes after atropine sulphate (0.0012 gm. subcutaneously): auricular rate, 80; ventricular rate, 80; and P-R interval, 0.24 sec.

Fig. 7.—Patient sitting (after six weeks with atropine sulphate medication, 0.0006 gm. orally three times a day): P-R interval, 0.22 sec.; and rate, 84.

by a series of roentgen ray films taken at various angles, was found to be normal. Lipiodol instilled into the trachea showed no abnormality of the larger air passages. The normal contour of the esophagus was revealed under the fluoroscope after barium was swallowed.

In view of these negative findings it was believed that the case was one of early heart-block of organic etiology, as indicated by a consistently prolonged P-R interval. The disease had apparently progressed to the

point where the function of conduction was barely adequate to permit all auricular impulses to pass through the bundle of His while the patient was erect.

The slight vagus effect always present on reclining or sitting, superimposed upon the organic lesion, was sufficient to magnify the block greatly. The supposition that the slowing of the ventricular rate was vagal in origin was demonstrated by its correction with small doses of atropine.

The effect of posture on the heart rate apparently varies in different individuals. It is generally believed that the difference in rates observed in the lying and sitting positions is due to pressure effects on the carotid sinus. The further difference that occurs between the sitting and the standing positions is thought to be due to another mechanism as yet not agreed upon. MacWilliam³ has recently discussed the problem and reviewed the relevant literature. In the above case it is not clear why pressure on the neck did not have a pronounced effect on the rate, when the effect of posture alone was so pronounced.

One other observation somewhat similar to that recorded here was made by Erlanger⁴ in 1905. He described a patient with complete heart-block, in whom there was a rise in auricular rate only on assuming the upright position. Under antisyphilitic treatment there was gradual release of the block. When this had assumed the phase of a 3:1 ratio, both the auricle and the ventricle beat faster with the patient standing. Moderate exercise also brought about a proportionate increase in the rates of each ventricle when the block was both complete and partial. Severe exercise, however, caused partial heart-block to become more complete.

It is presumed that our patient was seen at a period during the progression of an organic heart-block in which the vagus influence now plays an important part. This rôle may become less as the lesion progresses. It is entirely possible that similar occurrences with heart-block are not infrequent.

SUMMARY

A patient with partial heart-block, presumably of organic nature, had a ventricular rate much faster in the upright position than when recumbent. It appears that this discrepancy is due to vagus effect. Under atropine medication the block (other than a prolonged P-R interval) and its attendant symptoms disappeared.

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HEART-BLOCK FOLLOWING X-RAY TREATMENT FOR THYROTOXICOSIS*

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THE present study involves observations made upon a case of toxic goiter in which x-ray therapy was followed by the development of transient heart-block. Prolongation of the auriculoventricular conduction time in the presence of hyperthyroidism, although seldom recognized, was found by Goodall and Rogers⁸ in 242 of their 787 cases of goiter. Auriculoventricular dissociation, however, is very rare. In ten studies^{1, 2, 5, 8, 10, 11, 14, 17, 20, 21} in which electrocardiograms were made in a total of 1,844 cases of hyperthyroidism, complete dissociation was noted in only five instances. Individual cases in which Adams-Stokes attacks occurred as a complication of thyrotoxicosis have been reported by Merklen,¹³ Reilingh,¹⁵ and Carey.³ Incomplete block has been observed in two cases by Cameron and Hill² and in isolated cases by Lewis,¹² Simon¹⁶ and Easton.⁷ Complete block, confirmed by electrocardiogram, has been reported in two cases by Dameshek⁵ and in six cases by Davis and Smith.⁶

Although the view that hyperthyroidism characteristically improves auriculoventricular conduction has been denied by Joll⁹ on the basis of insufficient evidence, thyroid extract is nevertheless often used successfully in the treatment of Adams-Stokes attacks. Hyperthyroidism at least produces no apparent lesion to account for the occurrence of heart-block. Recent authors^{2, 3, 6} have therefore attributed the arrhythmia under the circumstances to intercurrent infection, to underlying organic heart disease, or to digitalis intoxication. The present case is remarkable for the absence of these factors, and in the mode of onset of the block it is apparently without precedent in the literature.

CASE REPORT

E. D., a young Italian woman, twenty-five years old, was admitted to St. Agnes Hospital on May 29, 1935, complaining of fainting attacks. Four years previously, she had first noticed an enlargement of the base of her neck and a tendency to unusual dyspnea and cardiac palpitation on effort. Nine weeks before admission she attended the out-patient department of another hospital to inquire about the swelling of the neck, stating that she was not nervous, had lost no weight, and felt in general quite well. On physical examination at that time, the only significant abnormalities were a goiter of moderate size, over which a bruit could be heard, slight exophthalmos, a coarse tremor of the hands, small but infected tonsils, and a soft systolic murmur at the cardiac apex. Five weeks later a metabolic rate test

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was reported as 40 per cent; on repetition a month later it was 25 per cent. The following week, however, a loss of five pounds in weight was considered indication for x-ray therapy, which was applied (200 volts, 8 milliamperes) for 18.2 seconds on May 6, and this was repeated on May 13. There was no significant reaction

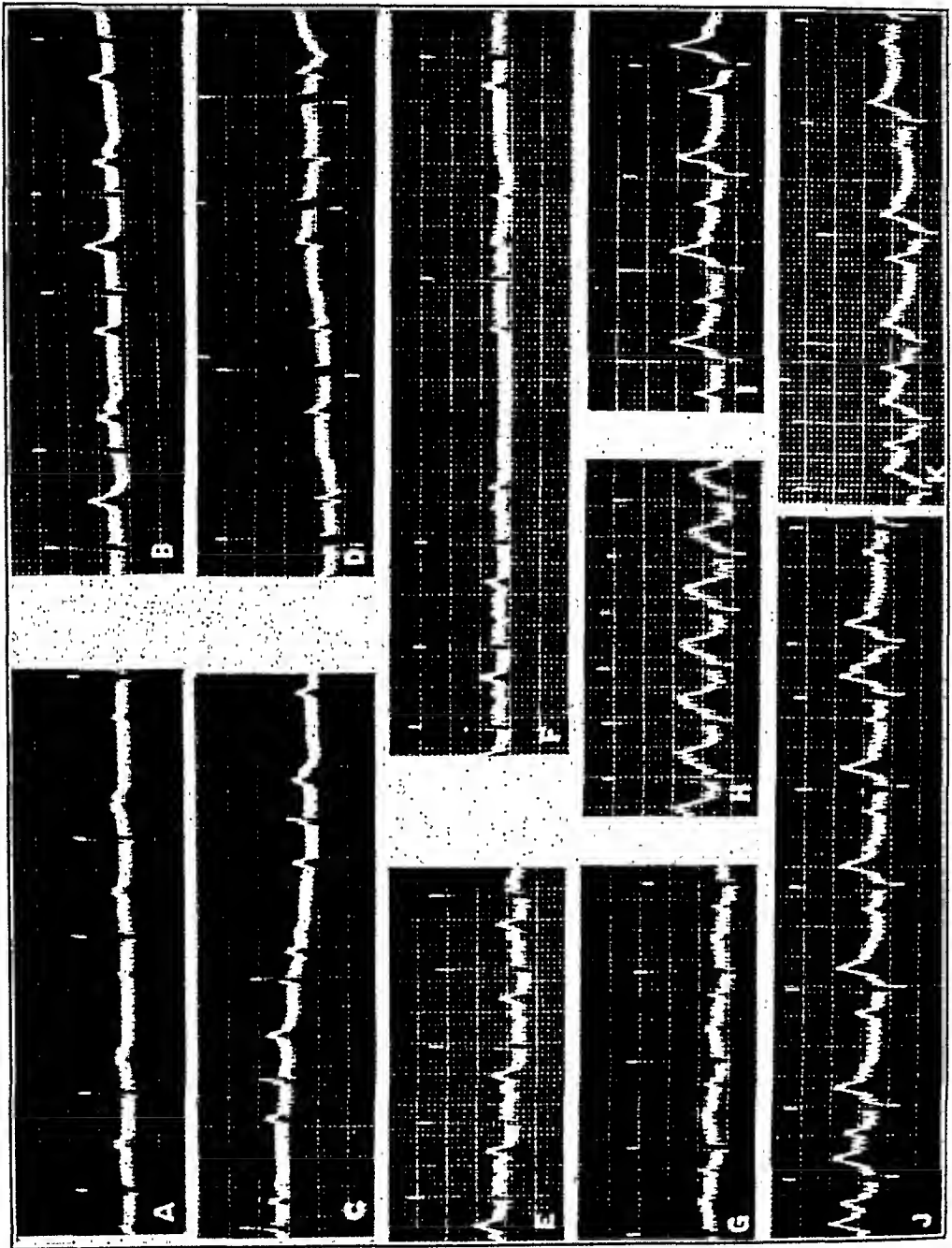


Fig. 1.

Fig. 1.—A, B, C, D: Leads I, II, III, and IV, respectively, of electrocardiogram showing 3:2 and 2:1 heart-block.

E, two days later, reversion to normal sinus rhythm with P-R intervals of 0.20 to 0.22 second (Lead II).

F, same, showing block produced by carotid sinus pressure.

G, eight days later, P-R intervals 0.16 second (Lead II).

H, same, tachycardia three minutes after adrenalin.

I, same, slowing of heart rate six minutes after adrenalin (P-R intervals 0.22 second).

J, same, sino-auricular block, nine minutes after the adrenalin injection.

K, same, bradycardia produced by carotid sinus pressure.

during treatment, but following the first application the patient "felt badly" and complained of pain in the thyroid region. After the second treatment these symptoms became worse, and two days later, on returning home from a visit to the nose and throat clinic, she became nauseated and fainted. Her temperature was subnormal; the pulse was slow and "jerky." She improved during ten days in bed but on getting up she was again subject to repeated fainting attacks for which she was brought two days later to St. Agnes Hospital.

The past medical history was negative for rheumatic infections. She had had measles, whooping cough, influenza, and many colds, but very few attacks of tonsillitis and no recent respiratory infections. The family and social histories were irrelevant.

Physical examination showed a pale, rather nervous girl weighing 109 pounds, with no dyspnea or cyanosis. There was slight exophthalmos and a positive von Graefe sign. The tonsils were cryptic and infected, but there was no acute pharyngitis. The teeth were in fair condition. Situated deep in the neck was a small nodular goiter about the size of a hazelnut, involving the right lobe of the thyroid, which was readily observed on swallowing with the head held in hyperextension. Pulsation of the carotid vessels was marked, but the jugular pulsations were disproportionately rapid. The lungs were clear. The heart was apparently normal in size, and there were no thrills, but the precordial pulsation was violent and diffuse. The rate was irregular, averaging between 40 and 60 per minute. The heart sounds were loud and booming but of good quality. At the apex a soft blowing systolic murmur was audible, transmitted to the base. The abdomen was normal. There was no ankle edema, but the hands presented a coarse tremor. The radial pulse was full with no deficit. The blood pressure was 100/70.

Laboratory examination showed a negative Wassermann reaction and a normal blood chemistry. Urinalysis gave a specific gravity of 1.029, a cloud of albumin, and a few hyaline casts and white cells. The blood count was hemoglobin, 67 per cent; R.B.C., 3,460,000; W.B.C., 7,400; neutrophils, 64 per cent; and lymphocytes, 36 per cent. The sedimentation rate was increased to 25 mm. per minute. Fluoroscopic examination showed the heart normal in size and contour. The metabolic rate test made three days after admission showed + 11 per cent. The electrocardiogram also made three days after admission showed an alternating 3:2 and 2:1 heart-block, the auricular rate averaging 110 and the ventricular rate 75. With the exception of a tendency to flattening of the T-waves in all leads there were no other significant abnormalities.

For the first five days the patient received Lugol's solution, three minims three times a day. The pulse rate increased from 40 to 80 by the fifth day, when medication was stopped to see if the block, which had disappeared, would return. The electrocardiogram now showed a normal sinus rhythm with a rate of 120 and rather prolonged P-R intervals of 0.20 to 0.22 second. On the eleventh day the P-R intervals were 0.16 second and the heart rate was 100. The T-waves in Leads I and II had definitely increased in amplitude. Examination of the heart showed no abnormalities other than the soft apical systolic murmur. Further convalescence was uneventful. The tonsils were removed without untoward effect. The patient was discharged in good condition on June 23, 1935, twenty-six days after admission, and since that time has had no abnormal cardiac signs or symptoms.

OBSERVATIONS

On admission the ventricular rate was much slower than when the first electrocardiogram was made three days later, and it is probable that at the onset of the arrhythmia there was a complete auriculo-

ventricular dissociation. On the fifth day when the second electrocardiogram was made, the block had disappeared except for prolongation of the P-R intervals which averaged from 0.20 to 0.22 second. At this time pressure applied to the carotid sinus produced a further prolongation of the P-R intervals to 0.28 second, followed by a 2:1 block. The auricular rate slowed from 115 to 70 and the ventricular rate to 35.

On the tenth day when the electrocardiogram appeared relatively normal and the P-R intervals measured 0.16 second, the effect of adrenalin was observed. With the patient seated, 1 c.c. of a 1:1,000 solution of adrenalin was given intramuscularly. The resting blood pressure was 114/75, and the pulse rate was 100. Within three minutes the blood pressure had increased to 160/90 and the pulse rate to 180. The electrocardiogram showed a sinus tachycardia with great increase in the height of the T-waves. At six minutes the rhythm became quite irregular due to transient periods of slowing of the heart rate to 100 accompanied by prolongation of the P-R intervals to 0.22 second. At eight minutes the P-R intervals had shortened to 0.16 second. At nine minutes the rhythm was interrupted by periods of sino-auricular block in which the rate slowed from 140 to 70 with occasional escape of isolated beats. At fourteen minutes the heart rate had returned to 140, and the block had disappeared. Pressure on the carotid sinus now produced slowing of the rate to 100 but no change in the auriculoventricular conduction time.

During this period of observation, the patient was not seriously uncomfortable and complained only of severe palpitation. She stated that the sensation was similar to that experienced after x-ray treatment of the thyroid and before the onset of syncope. Auscultation of the heart exhibited the loud booming sounds of hyperdynamic action but aside from the systolic murmur previously noted, no other abnormalities were apparent.

DISCUSSION

The cause of the heart-block in this case is not at once apparent. Since the action of digitalis can be excluded, there remain four agencies by which it might have been produced: systemic infection, organic heart disease, thyrotoxicosis, and hyperactivity of the vagus. There was, however, no evidence of infection. The patient exhibited no cough, fever, pharyngitis, or leucocytosis. Tonsillectomy failed to cause a recurrence of the arrhythmia. Likewise organic heart disease can probably be excluded in the absence of a history of rheumatism or the appearance of definite clinical signs. Thyrotoxicosis would seem to be the most likely explanation but for the fact that heart-block is exceedingly rare in this condition and is almost always explainable on the basis of other factors. Furthermore, the patient was not very "toxic"; the basal metabolic rate was only +11 per cent, and the mani-

festations of hyperthyroidism were relatively mild. One is led to assume therefore that an abnormal vagal effect was the factor primarily responsible for the arrhythmia.

Hyperactivity of the vagus as an explanation of the occurrence of heart-block in the present case is supported by the fact that the vagus is now generally recognized as a frequent contributory factor in heart-block⁴ and occasionally appears to be its sole mechanism.¹⁹ Simon¹⁶ attributed the occurrence of heart-block in his case to vagal damage sustained during thyroidectomy. A vagus effect is indicated in the present case by the fact that auriculoventricular dissociation could be reproduced by carotid sinus pressure in the initial period following the return of sinus rhythm.

The question arises as to the manner in which the vagus was affected. That stimulation was not due to pressure of the enlarged gland on the nerve trunk is certain from the absence of substernal goiter and the fact that digital compression of the gland failed to evoke any change in heart rate. Nor was any significant response elicited by swallowing or by ocular pressure. The logical conclusion is that excitation of the vagus was by way of the carotid sinus.

At the time when the P-R intervals were still prolonged, auriculoventricular dissociation could be produced by pressure on the carotid sinus. Later when the P-R intervals had become normal in duration, this procedure was without effect except for the characteristic slowing of the heart rate. Adrenalin was likewise ineffective in producing a recurrence of the block, except for a slight lengthening of the P-R intervals during the height of the rise in blood pressure. It appears, therefore, that the state of hyperactivity of the carotid sinus was a transient phenomenon. The only apparent cause was the x-ray therapy which it immediately followed and to which the carotid sinus was topically exposed. In other words, the carotid sinus, involved in the local application of x-rays to the thyroid, underwent a period of hypersensitivity which produced relative slowing of the heart rate at a time when the exacerbation of hyperthyroidism was at its height (auricular rate 110 in the first electrocardiogram as compared with 120 when the block had disappeared) and resulted in temporary auriculoventricular block.

The influence of the hyperthyroidism itself in the production of the block is uncertain. The frequently prolonged P-R intervals observed by Goodall and Rogers⁸ have not been noted by other authors, and they themselves found no actual dissociation. In the present case, the mildness of the thyroid symptoms and the fact that there is no known mechanism by which hyperthyroidism can produce heart-block seem adequate bases for the belief that the rôle of the thyroid was negligible.

Whether or not the sino-auricular block was in any manner related to the hyperthyroidism is likewise problematical. Sino-auricular block

is not uncommon in young people and is often produced by adrenalin or vagal stimulation so that its occurrence under the circumstances is probably not remarkable. Attention in passing is merited, however, by the recognition of heart-block as a possible concomitant of hyperthyroidism. Without an electrocardiogram the arrhythmia may easily be interpreted as a bradycardia, for which reason the correct diagnosis of hyperthyroidism may be overlooked.

SUMMARY AND CONCLUSIONS

1. A case is described in which transient heart-block with Adams-Stokes syndrome occurred following x-ray therapy for toxic goiter.

2. Soon after restoration of normal sinus rhythm, auriculoventricular dissociation could be brought on by pressure on the carotid sinus. Later both carotid sinus pressure and the injection of adrenalin were ineffective in reproducing the block although adrenalin still caused transient prolongation of the auriculoventricular conduction time.

3. On the basis of the evidence at hand it was concluded that the heart-block was caused by hypersensitivity of the carotid sinus resulting from exposure to x-rays.

4. Attention is called to the clinical value of recognizing heart-block as a possible cause of bradycardia in the presence of hyperthyroidism.

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PRIMARY TUMOR OF THE HEART

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TUMORS of the heart, both secondary and primary, are not often reported in the medical literature. The highly differentiated and specialized myocardium, however, sometimes is the seat of secondary tumors and occasionally of primary neoplastic growth. Secondary tumors, compared with primary tumors, are found in the proportion of 16 to 1. There are approximately one hundred fifty-five cases of primary tumor of the heart reported; of these about forty-five are classed as sarcomas. The literature on this subject was extensively reviewed by Perlstein¹ in 1918, and by Goldstein² in 1922. Since then only a few isolated cases have found their way into the literature. Most primary tumors are essentially not malignant, falling into the classification of fibromas, myxomas, lipomas, and rhabdomyomas. The following is a report of a histologically typical rhabdomyosarcoma.

REPORT OF A CASE

M. W., female, sixteen years old, was first seen on April 18, 1933, when she complained of shortness of breath and extremely rapid pulse. She appeared apprehensive; her pulse was rapid, 140 per minute, temperature, 98.8° F.; and respirations, 36 per minute. The heart beats were difficult to obtain with a stethoscope, the sounds appearing quite distant. The abdomen was rigid in the upper portion and the liver was depressed three fingerbreadths below the costal margin.

History of Present Illness.—Six days prior to entry to the hospital, the patient complained of diffuse pains in her abdomen and marked fatigue. On the day of entry she complained of some dyspnea which became progressively worse. She was taken to the hospital that night in extremis.

Family history was essentially negative. Past History: The child was healthy up until twelve months before the onset of the present illness. She had been rather athletic and enjoyed ordinary outdoor exercise. One year before the onset of the present illness the mother noticed that the child began to complain of feeling fatigued on any strenuous exercise, which prior to this time had been enjoyed. The family thought that it was probably laziness on the girl's part and would scold her for not taking a greater share in the housework. Her disposition up until this period had been very smooth, quiet and peaceful, but at times she would become rather indignant when the family insisted that she do certain tasks about the house.

Course in the Hospital.—The patient presented moist râles throughout both lungs, anteriorly and posteriorly. A diagnosis was made on entry of fulminating bronchopneumonia with cardiac failure. Adrenalin was given, together with morphine and atropine. This was followed by caffeine and digitalin stimulation. Oxygen

inhalations apparently gave some relief to the patient, but she failed to respond to therapy and died one hour and fifteen minutes after hospital entry.

Autopsy Report.—The body was that of a sixteen-year-old female appearing in a good state of nutrition. The skin generally had an especially marked florid appearance. The hair was abundant, abdomen distended, and extremities negative.



Fig. 1.—Illustration of heart showing tumor grossly confined to the auricles. The dark area is the point of gradual erosion and rupture of the auricular wall resulting in fatal hemorrhage. Because of this mass the auricle is almost entirely replaced by a solid tumor. Surface areas are nodular and friable and infiltrated by blood.

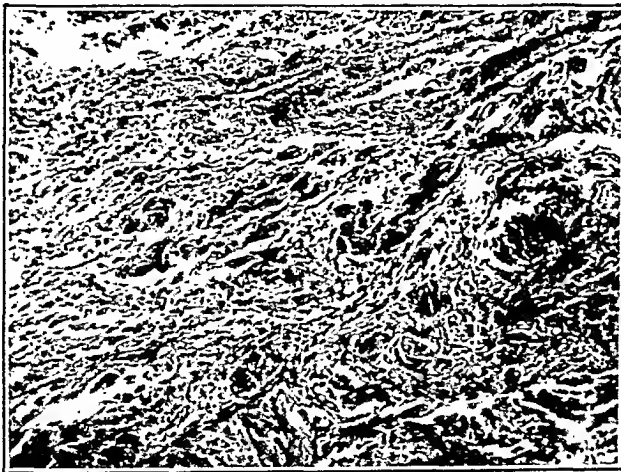


Fig. 2.—Low power picture of the tumor mass. Note the variation in size and shape of the cells with embryonic, immature characteristics. Resemblance to normal heart muscle fibers is well seen in some areas.

Upon opening the pleural cavities approximately 200 c.c. of serosanguineous fluid was found on each side. The heart had been pushed upward and backward by the tumor growth involving both auricles. Almost the entire area of both auricles was replaced by a nodular tumor growth, soft in consistency, somewhat friable, and markedly hemorrhagic. The auricular cavities were nearly filled by

the neoplastic process. Rupture had occurred in the region of the posterior aspect of the left ventricle, causing bleeding into the pericardial cavity. The pulmonary and aortic valves were not involved. Both the mitral and tricuspid valve rings were dilated, but smooth, and the valves themselves were not unusual. The weight of the heart was 880 gm.

The microscopic sections revealed an embryonic type of cell, small and fat spindle cells predominating. The cells were deep staining and showed mitoses. Giant cells were fairly numerous. There was some infiltration of both fresh red blood and old changed blood between the fibers, which gave the Prussian blue reaction for iron. There was microscopic invasion of the ventricular walls by the infiltrating tumor.

Both lungs were a beefy red in color and showed marked congestion. The microscopic sections revealed acute pulmonary edema with some passive congestion. Heart failure cells were in evidence showing a fairly long-standing process.

Liver: The liver was enlarged, firm in consistency and weighed 1700 gm. Cut section revealed a typical nutmeg appearance with marked bile stasis.

Pancreas: The pancreas was firm and somewhat fibrous and revealed on section a mild interstitial fibrosis.

The remaining organs and tissues apart from congestion revealed nothing noteworthy.

Diagnosis.—Primary rhabdomyosarcoma of the heart with rupture.

DISCUSSION

The tumor, although malignant, was confined to the heart. Like other reported cases of primary tumor of the heart, the site of origin was probably in the auricles. The ventricle walls on both sides showed microscopic infiltration but grossly appeared uninvolved. Death occurred from erosion of the left auricular wall with fatal exsanguination. This apparently was a slow erosion, with hemorrhage into the walls of the auricle as shown by the stasis of blood between the tumor fibers. Some of the spindle cells which appeared to be less embryonic showed areas of cross-striation. Mitoses were present, and giant cells were fairly common. Diligent search failed to reveal any evidence of tumor elsewhere in the body. This case, like the other reported cases we were able to study in the literature, was not diagnosed clinically before death.

REFERENCES

1. Perlstein, I.: Sarcoma of the Heart, *Am. J. M. Sc.* 156: 214, 1918.
2. Goldstein, H. I.: Tumors of the Heart, *New York M. J.* 115: 101, 158, 1922.

ELECTROCARDIOGRAPHIC CHANGES IN A CASE OF ELECTRIC SHOCK*

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THE following case is reported because of interesting electrocardiographic changes which occurred in rapid succession following electric shock. The changes occurred without clinically detectable structural cardiac disease or myocardial insufficiency.

CASE REPORT

W. C., white male motorman, thirty-six years old, was admitted to the Coney Island Hospital on the surgical service of Dr. Earl J. Miles† on Sept. 17, 1934. His family history was negative. His past history was likewise negative except for an electric burn in 1920.

While coupling two cars at about 6:00 A.M. on Sept. 17, 1934, he received a sudden electric shock which rendered him unconscious for about two minutes. He was admitted to the hospital shortly thereafter. Examination showed a well-developed young male, who did not appear ill. His respirations were normal. There was no cyanosis. The head and neck showed nothing abnormal. The heart was normal in size; the rhythm was totally irregular; and the sounds were of good quality. No murmurs were heard. The lungs were clear, and the abdomen was negative. Both lower extremities showed rather extensive second-degree burns.

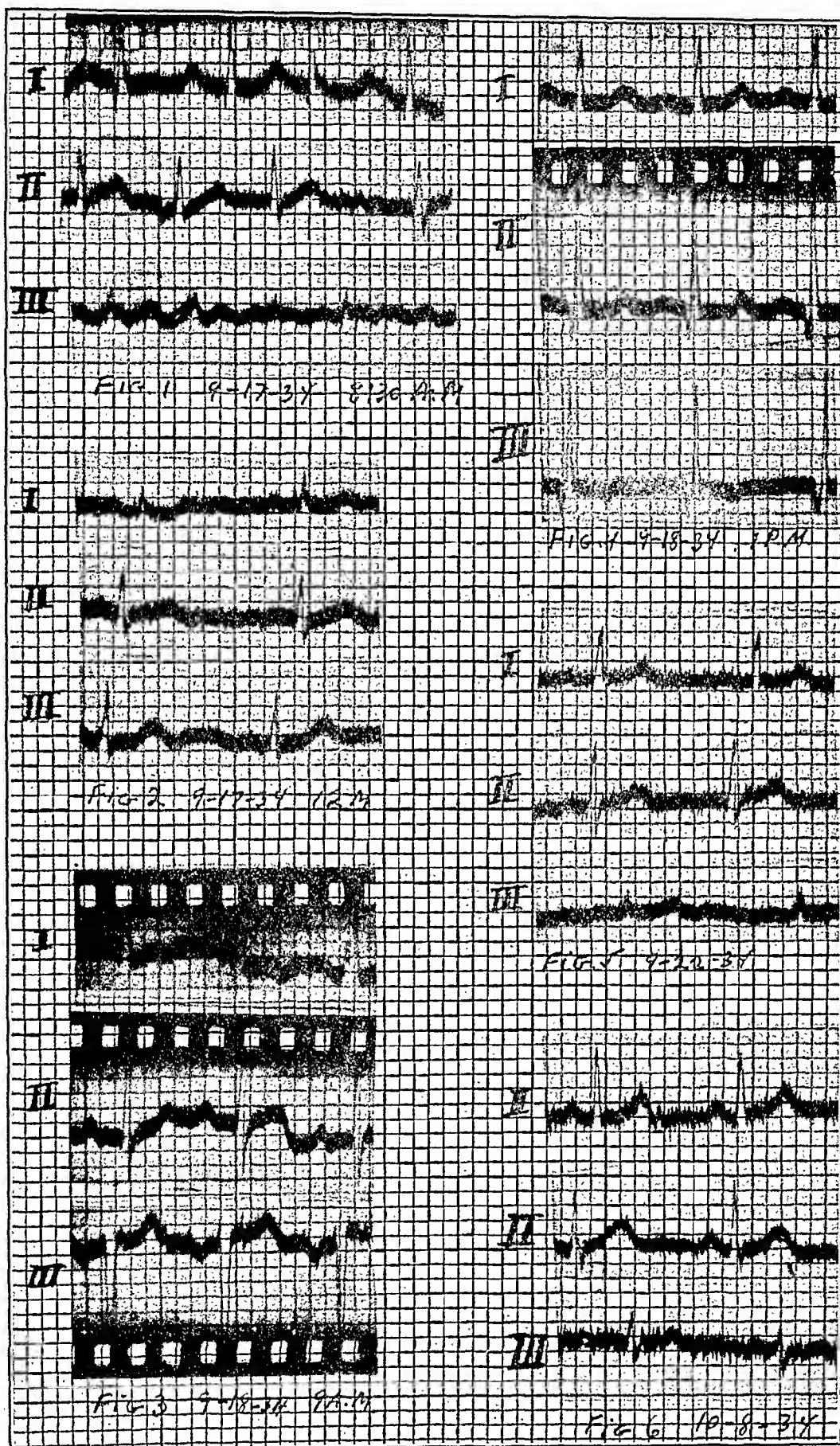
The total irregularity of the heart which he showed on admission persisted for about three hours, and then there was a return to the normal sinus rhythm which continued throughout his stay in the hospital. At no time did he show any changes in the heart sounds, any signs of cardiac enlargement, or the slightest suggestion of myocardial insufficiency. His temperature was normal throughout with the exception of an occasional rise to 100° F., which could be attributed to inflammatory reaction and absorption from the burns of the extremities. The laboratory findings including blood chemistry, blood Wassermann reaction, blood count, urinalysis, and x-ray findings were negative. He was discharged on Oct. 15, 1934, in a perfectly normal condition.

Electrocardiographic Findings.—An electrocardiogram (Fig. 1) was taken at 8:30 A.M., shortly after his admission to the hospital. It showed auricular fibrillation with a ventricular rate of about 110 and a tendency toward left axis deviation. At 12 noon the same day there was regular sinus rhythm with auricular and ventricular rates of about 75 per minute (Fig. 2). The P-R conduction time was about 0.16 sec. The QRS complex in Lead I was of comparatively low voltage while that of Lead III was of higher voltage than in the previous tracing.

At 9:00 A.M. the following day the P-R conduction time was increased to 0.20 sec.; the QRS complexes were of much higher voltage; and there was a marked degree of left axis deviation (Fig. 3). Lead I showed slight depression of the R-T segment and a negative T-wave, while in Lead III the T-wave was positive with slight elevation of the S-T segment. The P-wave was markedly negative

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†We are indebted to Dr. Miles for the privilege of reporting this case.



Figs. 1-6.

in the same lead. At 1:00 P.M. the same day the P-R conduction time was reduced to 0.16 sec., and the P-wave in Lead III became almost isoelectric with tendency toward the diphasic (Fig. 4). The left axis deviation had entirely disappeared. The previously negative T-wave in Lead I had become definitely positive while the positive T-wave in Lead III became negative. The S-wave which was present in Lead II before had disappeared, and a large Q-wave appeared in that lead as well as in Lead III. The QRS voltage was definitely increased in Lead II.

Four days later, on September 22, the tracing was essentially normal except for the QRS voltage, which was slightly lower than the accepted minimal normal (Fig. 5). There was a tendency toward left axis deviation, and the QRS and T complexes were similar to the first tracing. On October 6, sixteen days later, the tracing was similar to the one of September 22, with the QRS voltage reaching normal (Fig. 6).

COMMENT

The tracings were all taken with the patient in the same recumbent posture; shifting of the axis, as well as the changes in the complexes, cannot be attributed to any change in position of the patient. In the absence of any demonstrable clinical evidence of cardiac disease, the progressive, rapid electrocardiographic changes could be explained on the theory of disturbance in the electrical conductivity of the heart induced by the extrinsic electric current. Judging from the changes it is quite conceivable that the temporary unconsciousness of the patient for two minutes immediately after receiving the electric shock might have been due to temporary ventricular fibrillation which soon subsided.

Department of Reviews and Abstracts

Selected Abstracts

Cossio, P., and Menendez, E. Braun: Physiological Reduplication of the Heart Sounds. *Rev. argent. de cardiol.* 2: 149, 1935.

Even under normal conditions the physiological auricular heart sound, which is not audible as a rule, may be exaggerated and heard. This is the most frequent cause of the so-called "reduplication of the first sound."

When the third heart sound is perceptible in the second or third interspace, on account of its vicinity to the second sound, it may be taken as a reduplication of the latter.

By direct auscultation, the frequency of occurrence and the characteristics of the physiological reduplication of the heart sounds were determined in 100 individuals under perfect circulatory conditions. The group was formed of 25 children (5 to 10 years old), 25 adolescents (18 to 22 years old), 25 adults (35 to 55 years old), and 25 elderly people (70 to 110 years old).

Reduplication of the first heart sound was found in 15 out of the 100 persons, 2 children, 5 adolescents, 1 adult and 7 elders. Reduplication of the second heart sound was found in 20 (12 children, 7 adolescents, and 1 adult).

When the reduplication of the first heart sound occurred, both components occurred one immediately after the other, without intervening silence. The first component was always deeper and less intense than the second one.

In the cases of reduplication of the second sound there generally occurred a short silence, the first component being louder, snappier and higher than the second one.

The graphic registration of the heart sounds together with the electrocardiogram (in reduplicated first sound) or with the central venous pulse (in reduplicated second sound), of 22 patients with either first or second reduplicated heart sounds showed the following findings: Reduplication of the first sound was present in eight records; in three of them the second sound was also reduplicated. Reduplication of the second sound was found in fourteen cases besides the three already mentioned.

The records showed that in 62.5 per cent of the cases the first sound reduplication was due to the occurrence of an auricular sound. Asynchronous valvular play was probably the cause of the remaining cases. In both cases there was a true reduplication.

The records showed that in 69 per cent of the cases the reduplication of the second sound was only apparent, there really occurring a third heart sound more distinctly heard on the second or third left intercostal space, especially at the end of inspiration. In 23 per cent of the cases reduplication was considered as due to sigmoid asynchronism. In the remaining 17 per cent both a reduplication by sigmoid asynchronism and a third heart sound coexisted.

The suggestion is advanced that the third heart sound, better heard on the second interspace and accentuated during the final moments of inspiration, is a third sound originated in the right ventricle.

AUTHOR.

Roberts, George H., Crawford, J. H., and Abramson, David I.: **Experimental Bundle Branch Block in the Monkey.** J. Clin. Investigation 14: 867, 1935.

Following division of the left main branch of the His bundle in the rhesus monkey, the chief initial deflection of the electrocardiogram is upright in Lead I and downward in Lead III.

Division of the right branch results in initial deflections downwardly directed in Lead I and either upward or downward in Lead III.

Stimulation of the ventricle contralateral to the lesion produced complexes, the deflections of which corresponded in direction to those of the bundle-branch block.

The recorded data are further evidence in support of the new terminology of bundle-branch block localization.

AUTHOR.

Youmans, J. B., Akeroyd, J. H., Jr., and Frank, Helen: **Changes in the Blood and Circulation With Changes in Posture. The Effect of Exercise and Vaso-dilatation.** J. Clin. Investigation 14: 739, 1935.

The exchange of fluid between the blood and tissues, primarily controlled by capillary and colloid osmotic pressure, is greatly influenced by a number of secondary factors, particularly by posture. The great tendency to edema in the quiet erect posture is opposed by a rising colloid osmotic pressure and by an increasing tissue pressure in the feet and legs. These forces are aided by a decrease in the volume and velocity of the circulation in the legs. With muscular activity an even greater volume of filtrate than occurs on quiet standing is prevented from accumulating by a more active lymphatic drainage. Variations in these secondary factors will influence the exchange of fluid between the blood and the tissues and, in the presence of even slight changes in the serum proteins and capillary pressure, may determine the appearance or nonappearance of edema. Due consideration must be given to the influence of these secondary factors in interpreting the effect of abnormal variations in the fundamental forces concerned, especially under conditions of changing activity such as exist in ambulatory patients. For these reasons it is inadvisable to define too strictly the critical level of the serum proteins or venous pressure in relation to the pathogenesis of certain forms of edema.

AUTHOR.

Berliner, Kurt: **The Effect of Calcium Injections on the Human Heart.** Am. J. M. Sc. 191: 117, 1936.

Intravenous injection of 10 c.c. of a 20 per cent calcium gluconate solution produced changes in the electrocardiograms of twenty-six normal individuals.

These changes consisted of flattening or inversion of the T-waves in 92 per cent of the cases, flattening or inversion of the P-waves in 54 per cent, and marked bradycardia in 67 per cent.

Intravenous injection of 10 c.c. of physiological salt solution given to eighteen normal individuals had no effect whatsoever on the electrocardiograms.

This investigation, for the first time, supplies experimental proof of the effect of calcium on the normal human heart.

AUTHOR.

Levine, Harold D., and Levine, Samuel A.: **An Electrocardiographic Study of Lead IV With Special Reference to the Findings in Angina Pectoris.** Am. J. M. Sc. 191: 98, 1936.

In twelve instances in which the Q-wave was absent in Lead IV either at the left sternal border or at the apex, infarction of the ventricle was found. Two cases with bundle-branch block and one of tuberculous pericarditis with absent Q_s showed no infarction.

There were fifteen patients with small Q_4 (2 mm. or less), about half of whom had infarction and the other half did not.

Upright T-waves in Lead IV were found when no infarction was present and, in fact, where there was no significant heart disease.

In eleven cases in which the heart was normal and in one with posterior infarction, Lead IV was normal.

Evidence is presented to show that myocardial infarction is not uncommon in angina pectoris when there is no clinical evidence of a previous coronary thrombosis. Sixteen of 100 cases showed an absent Q_4 and in eleven of these the customary three leads were essentially normal.

Apart from the changes in Lead IV which occur during the acute phases of coronary thrombosis, the authors believe that the absence of Q_4 is very helpful in the diagnosis of a previous myocardial infarction, except when bundle-branch block is present.

Lead IV is indispensable in the proper diagnosis of certain cases of heart muscle disease.

AUTHOR.

Faulkner, James M.: *The Electrocardiographic Diagnosis of Acute Cardiac Infarction With Special Reference to the Value of Precordial Leads.* New England J. Med. 213: 1215, 1936.

In a series of electrocardiograms including precordial leads on 250 patients, a diagnosis of fresh cardiac infarction was made fifty-one times. In eight of these the diagnostic feature was present at some time only in the chest lead, and in three it was never present in the standard leads. A comparison between the electrocardiographic and the autopsy findings was made in thirty-three cases. Out of thirteen cases with acute infarction the electrocardiographic diagnosis was positive in eleven. Localization of the infarct was not reliable by the method used. Of the twenty patients who did not show infarction, four had a questionable electrocardiographic diagnosis, and in the remainder it was negative.

The findings here recorded support the following conclusions:

1. During the first two weeks after the development of cardiac infarction, the electrocardiogram is a highly accurate method of determining the diagnosis.
2. The precordial lead offers additional information of definite value in the diagnosis of fresh cardiac infarction.

AUTHOR.

Horn, Henry, and Saphir, Otto: *The Involvement of the Myocardium in Tuberculosis.* Am. Rev. Tuberc. 32: 492, 1935.

The literature of instances of tuberculosis of the myocardium is reviewed. Three main types can be differentiated, namely, the nodular, the miliary, and the diffuse infiltrative types. The last should be accepted only if either the histological changes undoubtedly are characteristic of tuberculosis or if the tubercle bacillus can be demonstrated either by guinea pig inoculation or by staining methods. Otherwise, this form of tuberculosis cannot be differentiated from the so-called specific productive myocarditis (Saltykow, Gierke). For similar reasons it is difficult to attribute to a tuberculous origin, fibrous myocardial lesions which may be present in the hearts of subjects dying of tuberculosis. Hence, the term chronic interstitial tuberculous myocarditis should be discarded.

Three instances of miliary tuberculosis of the myocardium are reported, one of which also revealed a conglomerate tubercle. These three instances occurred in children. The literature also discloses that the greater percentage of miliary tubercles in the myocardium occurred in children. This may indicate that the finding of

miliary tubercles in the hearts of young subjects dying of miliary tuberculosis is attended with less difficulty because of the relatively larger areas examined histologically.

AUTHOR.

Stevenson, Ralph R. and Turner, William J.: Rupture of a Papillary Muscle in the Heart as a Cause of Sudden Death, *Bull. Johns Hopkins Hosp.* 57: 235, 1935.

Nineteen cases of rupture of a papillary muscle in the heart have been reported in the literature. These cases have been summarized, and one more has been described. The usual cause is coronary occlusion and infarction of the myocardium. Rupture of the left anterior papillary muscle is usually preceded by occlusion of either the anterior descending branch of the left coronary artery or of the first descending branch of the circumflex portion of the left coronary. Rupture of the left posterior papillary muscle is associated with occlusion of both the right artery and the circumflex branch of the left coronary artery.

Sudden death occurred in half of the cases which have been reported. The condition might be suggested clinically by the sudden onset of a loud whistling to-and-fro murmur occurring in association with the signs and symptoms of coronary occlusion and cardiac infarction.

AUTHOR.

Sampson, John J.: The Prognosis of Bundle-Branch Block and Other Intraventricular Conduction System Lesions. *Am. J. M. Sc.* 191: 88, 1936.

One hundred and fifty-seven cases of classical bundle-branch block and 112 cases of heterogeneous atypical intraventricular conduction defect (as demonstrated by electrocardiograms) have been reviewed in an effort to estimate the prognosis of these groups.

Certain prognostic findings seem to characterize these groups and their elements. Especially to be noted is the high fatality occurring in cases of bundle-branch block during the first year after the discovery of the lesion or in the first 20 per cent of the life expectancy and the remarkable diminution of the case fatality rate in the groups which survive these periods.

AUTHOR.

Hamman, Louis, and Rienhoff, William F.: Subacute *Streptococcus Viridans* Septicemia, *Bull. Johns Hopkins Hosp.* 57: 219, 1935.

A man, thirty-five years of age, was ill with *Streptococcus viridans* septicemia without evidence of a valvular defect in the heart. There was a diagnosis of an arterial venous aneurysm between the external iliac artery and vein. In the absence of evidence of heart disease, it was decided that the *Streptococcus viridans* septicemia was originating from the infected focus in the walls of the aneurysm. At operation the aneurysm was ligated and removed. Following the operation there has been a complete recovery. A description of the specimen removed at operation is included.

Dana, Harold W., and Reidy, John A.: Mitral Valve Disease. *Pathological Report.* *Am. J. M. Sc.* 191: 109, 1936.

One-half of all cases of rheumatic endocarditis of the mitral valve show no stenosis of this valve at autopsy, even in cases known to have been of many years' duration.

Pure mitral stenosis is rarely found at autopsy, it cannot be recognized with certainty even when present, and modern physiological study would seem to suggest that the clinical importance of mitral stenosis is at present too much emphasized.

Pure mitral regurgitation is not uncommon, occurring in one-fifth to one-half of all cases of rheumatic endocarditis of this valve; it can of itself cause death, and it is believed that regurgitation is entitled to a more prominent place than it now holds in the study of mitral disease.

Clinical and pathological analyses were made of 150 cases of mitral endocarditis, after a preliminary study of about 300 hearts to establish standards for comparison.

One clinical case history, with autopsy findings, is presented.

AUTHOR.

Coburn, Alvin F., and Pauli, Ruth H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process. *J. Clin. Investigation* 14: 783, 1935.

The findings presented in earlier papers of this series led to two conclusions: First, both influenza virus and one type of hemolytic streptococcus were ineffective in initiating recrudescences in a rheumatic colony. This strain of streptococcus did not produce soluble toxin, and although present in the throat, flora was not associated with acute infection. Second, another type of hemolytic streptococcus was highly effective in initiating recrudescences in fourteen out of sixteen rheumatic members of this same colony. This strain was a strong toxin producer, was associated with acute infection of the upper respiratory tract, and was a single serological type. In addition to infection with an effective strain of hemolytic streptococcus, two other factors contributed to the development and character of this epidemic of acute rheumatism. These factors were, first, the disease pattern peculiar to each rheumatic subject, and second, the intensity of the immune response.

Next it was pointed out that most strains of hemolytic streptococcus which are effective in producing acute rheumatism form soluble toxin and streptolysin and are indistinguishable from scarlatinal strains. Most of the strains associated with throat infections which are ineffective in initiating rheumatic attacks form little or no soluble toxin. This finding, in conjunction with earlier studies, indicates a close relationship between scarlet fever, acute rheumatism and toxin-producing strains of hemolytic streptococcus.

The findings presented in the fifth paper of the present series demonstrated that neither active nor passive immunization to hemolytic streptococcus inhibited the development of the rheumatic process. The observations indicated that the development of rheumatic activity depends not only upon infection with an erythrogenic strain, but also upon the host's immune response to such infection.

Next it was pointed out that there is a close time relationship between the anti-streptolysin rise and the onset of rheumatic activity. A small number of rheumatic subjects were observed to be infected with strains of hemolytic streptococcus which produced strong toxin and streptolysin and nevertheless failed to develop a significant rise in antistreptolysin titer. These individuals also failed to develop a rheumatic attack. The authors interpret this fact to mean that, in addition to infection with an effective strain, stimulation of the host sufficient to produce an antibody response is essential to initiation of rheumatic activity. It seemed that the character of the antibody response played a large part in determining the type of the rheumatic attack.

Finally, the observations made in the present paper indicate that in the patients who escaped postsplenectomy rheumatic recrudescences, the antibody-producing tissue was presumably quiescent; and that in those patients who developed acute rheumatism following splenectomy, the antibody-producing tissue was probably in a state of activity. Likewise, as was already pointed out, in the subjects who escape recrudescences following infection with hemolytic streptococcus, the antibody-pro-

ducing tissue presumably remains quiescent; and in those subjects who develop acute rheumatism following hemolytic streptococcus infection, the antibody-producing tissue is activated. These two sets of observations together show that acute rheumatism may follow either activation of the antibody-producing system by hemolytic streptococcus or operative manipulation of this system during the period in which it is producing immune bodies to hemolytic streptococcus.

It is the authors' conception that rheumatic disease is the result of the following sequence of events: (1) Infection with toxin-producing strains of hemolytic streptococcus initiates a process peculiar to rheumatic subjects. (2) In the course of this process a substance is released, presumably from the antibody-producing tissues, which either directly or indirectly alters mesodermal structures. This substance is probably not the infecting organism, and at the present time there is no evidence to suggest that it is viable. (3) The release of this toxic substance seems to take place only when there is an immune response to hemolytic streptococcus.

In conclusion, the collected evidence indicates that activity of the rheumatic process depends not only upon effectiveness of the infecting strain of hemolytic streptococcus but also upon the intensity of the immune response of the rheumatic subject to this bacterial agent.

AUTHOR.

Blackford, L. Minor: Syphilitic Aortic Insufficiency. *J. M. A. Georgia* 24: 341, 1935.

Seven cases of syphilitic aortic insufficiency representing about 5 per cent of the total series studied led to the following conclusions:

Syphilis of the aorta can be prevented by the thorough treatment of every case of syphilis in its early stages. In spite of the two cases reported in which it was apparently beneficial, the use of neoarsphenamine in the usual dosage in the treatment of syphilis of the aorta is fraught with grave danger.

An occasional patient with syphilitic aortic insufficiency will live comfortably for a number of years without any treatment. Careful regulation of the mode of living, treatment with bismuth, potassium iodide, and digitalis will often serve to make the patient with syphilitic aortic insufficiency more comfortable, and probably permit him to live longer.

AUTHOR.

Taussig, Helen B.: Essential Hypertension in Boy Two Years of Age, *Bull. Johns Hopkins Hosp.* 57: 183, 1935.

The case is that of a two-year-old colored boy with hypertension, cardiac enlargement, and progressive cardiac failure. The hypertension was present throughout the period of observation, and probably had already existed for several months. The autopsy yielded little, if anything, of a positive nature to explain the hypertension. The lesions in the kidneys appeared to be too slight, too widely scattered, and of too recent origin to form the basis for the known duration of the hypertension.

Menendez, E. Braun, and Orias, O.: Duration of Phases of the Cardiac Cycle in Hypertension. *Rev. argent. de cardiol.* 2: 186, 1935.

The duration of the cardiac phases was determined from the venous pulse recorded in twenty-six patients with arterial hypertension and in thirty normal persons.

The duration of the phases of the cardiac cycle in patients with arterial hypertension showed significant differences as compared with that of the normal individuals.

Total systole is prolonged, especially at the expense of the ejection phase ($+ 0.03 \pm 0.005$ sec.), whereas the isometric contraction is reduced (0.04 ± 0.002 instead of 0.05 ± 0.002 sec.). The difference (0.04 ± 0.005 sec.) is significant.

AUTHOR.

Cranch, A. G.: Hypertension With Relation to Capacity for Work. Ohio State M. J. 31: 676, 1935.

Hypertension is probably more common in industry than is generally supposed. Care must be taken to avoid error in detection of cases. Itself only a symptom, associated conditions must receive the greatest consideration. From the point of view of capacity for work, myocardial and arteriosclerotic changes are most important. Standards based primarily on blood pressure determinations are not satisfactory. Successful placement of hypertension cases is possible only through continuing supervision.

It is believed that the findings with regard to diastolic pressure are commonly of more significance than those of systolic pressure in estimating the capacity for work. Particular attention should be given to cases which show steadily rising pressures on succeeding examinations, and those cases which show evidence of myocardial deficiency or marked arteriosclerotic changes.

AUTHOR.

Wartman, Wm. B.: A Study of the Venous Blood Pressure in Some Common Diseases, Am. J. M. Sc. 190: 464, 1935.

1. The results of 366 determinations of the venous blood pressure in 215 patients suffering from various diseases have been presented.

2. In a control series of thirty-one patients who showed no evidences of circulatory disease, the average venous pressure was 83 mm. H_2O , and the difference of the two readings with the standard deviation of the difference was 16 mm. H_2O = 11 mm. H_2O .

3. An increase in venous pressure was observed only in patients suffering from cardiac failure with congestion or mediastinal obstruction.

4. Serial determinations of the venous pressure were of value in following the course of cardiac cases; a shift toward the normal indicated a favorable prognosis, but a progressive increase in pressure was an unfavorable sign.

5. The arterial and venous blood pressures appear to be independent, in the sense that a change in one does not necessarily affect the other.

6. The presence of pulmonary tuberculosis, bronchial asthma, or lobar pneumonia did not influence the venous pressure of the cases studied.

7. When an increase in venous pressure occurred in any disease, it usually indicated beginning circulatory failure.

8. Of the patients with a venous pressure over 250 mm. H_2O , 69 per cent died within three months, whereas only 8 per cent of those with a pressure below this critical level succumbed.

AUTHOR.

Head, Jerome R.: Effect of High Intrapleural Pressure on Blood Pressure. Arch. Int. Med. 56: 904, 1935.

It can be said that high pressure in the pleural cavity acts directly on both the pulmonary and the systemic circulation, on the former by collapsing the lung and on the latter by compressing the great veins.

Collapse of the lung causes: (1) a decrease in the flow of blood throughout the collapsed lung, (2) a rise in pressure in the pulmonary circulation, (3) an increased strain on the right heart, and (4) a reduction in the vital capacity.

Compression of the great veins causes: (1) a rise in the venous pressure, (2) an insufficiency in the return of venous blood, and (3) a decreased output of the heart.

Up to relatively extreme degrees of pressure these hindrances are compensated for by an increase in tone of the vasoconstrictor center. The first sign of the strain on this compensatory mechanism is an exaggeration of the Traube-Hering waves, a tendency for the peripheral resistance to give way during inspiration. A time comes when the center can no longer fully compensate, and the mean blood pressure falls below the critical level.

AUTHOR.

Marinescu, G., Bruck, H. A., and Vasilescu, N.: Capillary Circulation in Organic Hemiplegia. *Ztschr. f. Klin. Med.* 127: 578, 1934.

In the affected extremities of organic hemiplegia the following vasomotor and humoral changes were observed: (1) dilated capillaries in which there was a slower blood flow; (2) slower refilling of the capillaries after compression (20-21 seconds) than in the normal subjects (15-17 seconds); (3) diminished absorption capacity of the capillaries and veins after compression; (4) reduction and retardation of active dilation of blood vessels after compression; (5) increased alkalinity of the blood (5.7-11 per cent); (6) lowering of the viscosity of the blood; (7) presence of edema and acrocyanosis due to change of tonus in the peripheral blood vessels; and (8) abnormal dilation of the vessels in the affected extremity following the injection of calcium.

J. K.

Urban, H.: Arteriography of the Brain. *Wien klin. Wchnschr.* 48: 924, 1935.

Arteriography of the brain is valuable from the diagnostic standpoint when the neurological findings do not indicate clearly the type and location of the brain lesion. No reactions were noted as a result of the use of the thorotrast for arteriography following the technique of Moniz. Ten cubic centimeters of thorotrast are injected into the internal carotid artery after it is exposed by incision. Injection must be made quickly, and the picture must be made immediately thereafter as the thorotrast disappears from the brain after three seconds.

J. K.

Herrmann, L. G.: Nonoperative Treatment of Inadequate Peripheral Distribution of Blood: Passive Vascular Exercises and Local Hyperthermia. *J. A. M. A.* 105: 1256, 1935.

The results of passive vascular exercises (pavax therapy) in dealing with suddenly or gradually occluded arteries of the extremities have been evaluated by Herrmann and found satisfactory. The author draws his conclusions from some 50,000 hours of pavax therapy given to several hundred patients in the first thirty-three months of its use in his clinic.

One of the most remarkable results obtained has been in preventing the serious sequelae of extensive thermal trauma to the extremities in all cases treated by this method.

Herrmann emphasizes the object of the treatment, to develop adequate collateral circulation around the obstructed artery or arteries; and likewise the fact that clinical judgment must be used in selecting cases. Sudden obliteration of major arterial pathways offers the most opportunity for striking clinical benefit.

In thromboangiitis obliterans, Herrmann believes the method offers only temporary relief due to the extensive obliteration of arteriolar and small arterial beds which characterizes the disease.

For the past year preheated dry air at an average temperature of 104° F. (local hyperthermia) has been combined with the pavaex therapy with encouraging effect. This is thought to be due in part to the release of concomitant vasospasm, in part to increase of the metabolism of the tissues as the collateral blood supply is simultaneously augmented.

L. H. H.

Reimann, F., and Breuer, A.: Venesection Therapy of Polycythemia Vera. *Ztschr. f. klin. Med.* 128: 238, 1935.

Systematic venesection was used in seven cases of polycythemia vera. Three hundred to five hundred cubic centimeters of blood were withdrawn twice weekly until the hemoglobin in the blood was lowered to 80 or 90 per cent. The repeated bleedings reduced the number of circulating erythrocytes and relieved the patients of their subjective complaints. Venesection is not only symptomatic therapy, but at the same time it attacks the principal mechanism of blood regeneration by reducing reserve material, principally iron, which is necessary for the production of red cells and hemoglobin. In several cases total remission of polycythemia was observed, and one patient remained without complaints for three years. The result of repeated venesection in polycythemia proved to be equal to, if not superior to, the usual therapy with x-rays and phenylhydrazine.

J. K.

Johnson, Carl A.: Studies of Peripheral Vascular Phenomena: IV. The Effect of Artificial Fever on the Pulse Volume Changes of the Finger, *Am. J. M. Sc.* 190: 485, 1935.

The effects of artificial fever upon the peripheral circulation have been presented and may be briefly summarized as follows:

1. There was a marked increase in the pulse-volume changes of the fingers with all types of artificial fever used, except foreign protein which gave a primary decrease associated with the chill, but followed by an increased circulation.

2. The vasodilatation of foreign protein fever is probably of central origin while the vasodilatation with artificial fever induced by external heat and preventing heat loss is chiefly of peripheral origin.

3. The maximum increased circulation from artificial fever occurred in general at temperatures between 103° and 104° F. while the maximum temperature used was 104.5° F. This suggests that there is an optimum temperature at which peripheral circulation reaches a maximum.

4. Artificial fever from external heat and prevention of heat loss is dangerous and should not be used unless adequate facilities are available and should not be left in the hands of a technician.

Atchley, Dana W.: The Role of Peripheral Circulatory Failure in Clinical Medicine, *New England J. Med.* 213: 861, 1935.

In this address before the New England Heart Association, the author describes the picture of peripheral circulatory failure from varying causes, especially those conditions without cardiac failure. He believes that dehydration and salt depletion account for the picture of peripheral circulatory failure and for the classical syndrome of shock. He believes that an estimation of venous pressure is of importance

in differentiating this type of shock from cardiac failure. He describes briefly the treatment for the condition, emphasizing the need for the restitution of salt, together with the introductions of serum protein by means of transfusion of blood or other colloidal substances, such as acacia.

AUTHOR.

Veal, J. Ross, and McFetridge, Elizabeth M.: Primary Thrombosis of the Axillary Vein. An Anatomic and Roentgenologic Study of Certain Etiologic Factors and a Consideration of Venography as a Diagnostic Measure. *Arch. Surg.* 31: 271, 1935.

Two cases of primary thrombosis of the axillary vein are presented. Roentgenological and anatomical studies prove clearly that constriction of the vein occurs, not as previously believed over the first rib beneath the subclavius muscle, but below the head of the humerus and against the subcapsularis muscle. The stretching of the vein takes place only within the part of the vein just proximal to the point of constriction below the head of the humerus. The emptying time of the vein is actually more rapid in the position of hyperabduction and external rotation than when the arm is held at an angle of 45 degrees to the body. The increase in the venous pressure is brought about not by change of position itself but only when additional factors of strain are introduced. However, the etiology of primary axillary vein thrombosis has not been determined, although the reasonable assumption is that the constant underlying factor is some individual anatomic variation. Venography allows clear delineation of the obstructed area and of the pathways through which blood flows toward the heart.

E. A.

Anrep, G. V., and Von Soalfeld, E.: The Blood Flow Through the Skeletal Muscle in Relation to Its Contraction. *J. Physiol.* 85: 375, 1935.

Muscular contraction is accompanied by compression of intramuscular blood vessels. This compression and subsequent vasodilatation depend on the strength of the muscular contraction. Potent vasodilating substances appear in the venous blood emerging from a contracting muscle. They are produced and released during muscular contraction and are stable in the blood for half an hour at least.

E. A.

Nicole, R.: Arteriospasm in Acute Thrombosis of the Veins. *Schweiz. med. Wchnschr.* 65: 676, 1935.

The presence of a spastic occlusion of the femoral artery resulting from acute thrombosis of the femoral vein is described. The femoral artery was contracted for several hours. The skin showed signs of ischemia. Such cases are often mistaken for arterial embolism and are operated on without success. The arterial spasm is perhaps due to a regulating mechanism for averting increased blood supply which could not be carried away by the closed vein. Therapy consists of rest, elevation, and heat.

J. K.

Clark, Eliot, R., and Clark, Eleanor Lintow: Observations on Changes in Blood Vascular Endothelium in the Living Animal. *Am. J. Anat.* 57: 385, 1935.

Observations on blood vessels in living amphibian larvae and in transparent chambers inserted in rabbits' ears indicate that endothelium undergoes a series of changes.

Phase 1.—The lining is smooth; tonicity, elasticity, and contractility (amphibians only) are present.

Phase 2.—No impairment of tonicity, elasticity, and contractility. The consistency of the endothelium changes slightly and leucocytes may stick to the wall momentarily.

Phase 3.—Endothelium becomes sticky and leucocytes cling to the walls. Tonicity and elasticity are not impaired.

Phase 4.—Consistency of endothelium becomes softer; leucocytes push through to outside tissue.

Phase 5.—Endothelium is subjected to mechanical or chemical injury. Tonicity and elasticity are lost, and leucocytes lose their mobility.

Phase 6.—Serious injury to the endothelium which causes it to separate into solid, rounded, hyalin globules which are ingested by macrophages. Endothelium damaged this badly does not recover.

The rapidity with which changes in endothelial consistency may take place and the relatively minute stimuli necessary to elicit certain of these changes, together with their reversibility, are of unquestionable physiological importance and should be taken into account in any comprehensive consideration of the morphology and physiology of blood vascular endothelium.

E. A.

Montgomery, A. H., and Ireland, J.: Traumatic Segmentary Arterial Spasm. J. A. M. A. 105: 1741, 1935.

After experiencing two instances of spasmodic occlusion of the normal brachial artery in the vicinity of a fracture, proved by operative exposure, the authors searched the literature for reports of similar alarming episodes. They found the condition reported infrequently, and almost exclusively by continental European surgeons.

The reports, as in their own cases, dealt only with large arteries of the extremities, which remained bloodless cords for minutes to hours for a varying distance from the site of trauma. Gunshot wounds and fractures were blamed for thirty-six of the forty-four cases investigated.

The spasm generally relaxed within twenty-four hours. In those cases in which the occluded portion was excised, thrombosis was never found. The condition is considered due to a sympathetic nerve imbalance causing the spasmodic constriction, or possibly, in the light of recent work, to a chemical factor released by the trauma.

The authors advise conservative measures of treatment at first, and if the circulation does not return after reduction of the fracture or care of the wound, then exposure of the artery and application of continuous warm moist dressings.

L. H. H.

Ross, J. P.: The Results of Sympathectomy. An Analysis of the Cases Reported by Fellows of the Association of Surgeons. Brit. J. Surg. 23: 433, 1935.

About 250 records of various types of operation on the sympathetic nervous system were submitted, one-fourth of which were adequate to show late results of sympathectomy. Ganglionectomy was invariably successful in sixty-one cases of Raynaud's disease unless complicated by scleroderma.

In thromboangiitis obliterans, with intermittent claudication only, the effect of ganglionectomy was slight or nil in twenty-nine instances reported. Rest pain was relieved and gangrene arrested in a majority of thirty-seven cases of that disease. Clinical criteria for choice of patients did not show up clearly in the reported cases.

The results of sympathectomy applied to other pathological states including poliomyelitis-paralyzed limbs with circulatory disorders, Hirschsprung's disease, renal pain, and causalgia were more good than otherwise. Even periarterial sympathectomy in twenty cases of gangrene brought relief of pain or unexpected arrest of several of the gangrenous processes.

Indeed, the results of the analysis bespeak a care in selection of cases for sympathetic system surgery and a technical efficiency which are remarkable. One can only hope that later reports on follow-up and a more extensive series of cases will turn out as well.

L. H. H.

Burge, W. E., Orth, O. S., Neild, H. W., Ash, J., and Krouse, R.: Mechanism of Pathological Calcification. *Arch. Pathol.* 20: 690, 1935.

The authors recall briefly some of the recent theories of calcification in the soft tissues of the body. The suggestion is then made from their experimental results that the electronegativity of active, injured or dying tissue is due to negatively charged phosphate ions at the site. A demarcation current set up by the difference in potential between cut or injured surface of tissue and an uninjured or inactive portion was abolished by applying positively charged calcium or barium ions to the injured area. This is considered due to the combination of the positively charged ions with the negatively charged phosphate ions to form insoluble and nonionized barium or calcium phosphate.

The method was applied to the injured intima of arteries, and the same results occurring, the authors attribute pathological calcification of arteries to the insoluble calcium phosphate thus precipitated at the point of injury of the wall.

L. H. H.

Perlow, S., and Vehe, K. L.: Variations in the Gross Anatomy of the Stellate and Lumbar Sympathetic Ganglia. *Am. J. Surg.* 30: 454, 1935.

The authors, stimulated by the recent growth of surgical procedures involving the sympathetic nerves and ganglia, dissected out the stellate and lumbar ganglia and immediate connections in twenty-four cadavers. They present, with the aid of drawings, the variations in size, position and connections of the ganglia which they observed.

L. H. H.

Rusznayak, S., Karady, I., and Ezaba, D.: Experiments to Prevent Postoperative Shock Syndromes. *Deutsche med. Wchnschr.* 61: 1111, 1935.

Patients who are predisposed to postoperative shock show a characteristic blood pressure reaction after injection of 0.005 mg. histamine intravenously. The systolic blood pressure is diminished for a short time following the injection of histamine and then increases greatly. Subcutaneous injections of 0.5 to 1 mg. of histamine for several days in succession can change this type of reaction to one in which there is no increase in the blood pressure. It would seem that repeated injections of histamine before operation might prevent circulatory collapse which may follow operation.

J. K.

Voelker, Heinrich: Examination of the Circulation Time in the Lung. Determination of the Shortest Lung Circulation Time. *Ztschr. f. d. ges. exper. Med.* 96: 482, 1935.

In experimenting on the lungs of cats, to determine the circulation time, the modified Stewart method was used— injection of glucose into the jugular vein. The time which is necessary for the glucose to reach the carotid artery is the circulation time in the lung. The difference in the time when glucose can be

identified in blood from the femoral and carotid arteries is the circulation time in the aorta. The average circulation time of the lungs was 3.2 seconds; the rate of circulation in the aorta was 12 meters per second. Chloroform used as an anesthetic instead of ether increased the circulation time in the lung by 2 seconds and slowed down the circulation in the aorta to 4 meters per minute. Avertin administered by rectum did not change the circulation time of the lung. Inhalation of CO₂ slightly lowered the circulation time of the lung and increased the circulation in the aorta. Bloodletting changed the lung circulation only very slightly. After eventration there was a slight decrease in the aorta circulation time, but the lung circulation stayed nearly unchanged. This shows that the lung circulation is kept nearly constant by the organism in spite of great changes in the general circulation.

J. K.

McGovern, T., McDevitt, Ellen, and Wright, Irving S.: Theobromine Sodium Salicylate as a Vasodilator. *J. Clin. Investigation* 15: 11, 1936.

Twenty patients suffering from one or more of various peripheral vascular diseases were studied to determine the claims made for theobromine and its salts as efficient vasodilators, suitable for use in the treatment of peripheral vascular disease. Patients were studied under standard controlled environmental conditions, and the effect of the drug on skin temperature of various parts of the body, pulse, respiration, and blood pressure changes was noted.

It is concluded from this study that theobromine sodium salicylate in the dosage and by the methods of administration used is too unreliable and feeble a vasodilator to be of value in the treatment of peripheral vascular disease.

AUTHOR.

Resnik, Harry, Jr., Friedman, Ben, and Harrison, T. R.: Effect of Certain Therapeutic Measures on the Cardiac Output of Patients With Congestive Heart Failure. *Arch. Int. Med.* 56: 891, 1935.

The cardiac output per minute of persons with congestive heart failure tends to be decreased by rest, venesection, morphine, thyroidectomy, and abdominal paracentesis. In proportion to the metabolic needs the output may or may not be diminished by these procedures.

In patients with auricular fibrillation the restoration of the normal rhythm with quinidine has been associated with an increase in the cardiac output.

Resection of the pericardium of a patient with obliterative pericarditis was followed by an increase in the cardiac output.

The mechanism of improvement produced by the various therapeutic measures has been discussed. It is concluded that pericardial resection produces improvement in patients with concretio cordis by allowing the heart to do more work. On the other hand, therapeutic benefit in heart failure of the ordinary type is believed to be dependent on one fundamental factor: rest of the heart as a result of diminished expenditure of energy. Such an effect may be brought about either (a) by procedures which diminish the work done by the heart or (b) by measures which increase its mechanical efficiency so that less energy is wasted.

AUTHOR.

Carr, James G., and Mayer, Jacob D.: Clinical Experience With a Derivative of Squill, *Arch. Int. Med.* 56: 700, 1935.

Seillonin, a derivative of squill, will produce the usual effects of digitalis in the treatment of cardiac decompensation. Essentially the same therapeutic and toxic results are obtained as occur with the use of digitalis.

Cardiac irregularities are likely to be the first signs of dangerous intoxication. Nausea does occur and may precede the appearance of cardiac irregularities. The

nausea of scillonin intoxication is significant in that it appears to signify a more advanced grade of intoxication than that associated with the nausea of digitalis. Nausea and cardiac irregularities occurring in the course of treatment with scillonin are symptoms which call for the immediate discontinuance of administration of the drug.

Slowing of the cardiac rate to 60 or below is frequent with the successful use of scillonin. The onset of a rate as low as 60 is significant of the full therapeutic dose and calls for discontinuance of scillonin medication temporarily.

A dose of from 8 to 12 mg. of scillonin of standard potency as now provided, depending on the weight of the patient, may be given within four days to patients who are known to have taken no drug of the digitalis group within two weeks. If a prior course of scillonin or of some other drug of the digitalis group has been used with full therapeutic effect, the maximum dosage of scillonin should not be repeated within a month. Under these circumstances small doses may be given daily until the effect appears. The maintenance dose of scillonin is approximately 0.5 mg. per day, but it must be adapted to the needs and response of the individual patient. In a few cases in private practice the patient has been kept on a small daily ration for three years or more. For small patients the daily maintenance dose is as low as 0.33 mg.

Scillonin therapy is of advantage to certain persons who take digitalis with difficulty because of gastric distress early in the course of medication. Scillonin may be recommended for these patients. It is not a substitute for digitalis in the presence of frank digitalis intoxication. When digitalis has been given recently, only small doses of scillonin are permissible. The desired effect may be achieved by daily doses somewhat larger than the maintenance dose.

Scillonin retains its potency over a long period. A supply known to be about seventeen months old proved as effective at the end of that time as the lots recently assayed.

AUTHOR.

Dieuaidé, F. R., Tung, C. L., and Bien, C. W.: A Study of the Standardization of Digitalis. I. A Method for Clinical Standardization. J. Clin. Investigation 14: 725, 1935.

Past efforts to standardize digitalis by clinical study are briefly reviewed.

An attempt was made to ascertain the feasibility of separating by clinical assay different strengths of the same tincture of digitalis. In the conditions of the experiments, among the phenomena observed (which included symptoms, weight, blood pressure, cardiac rate, and various aspects of the electrocardiogram), only one seemed clearly helpful. The effect, under standard conditions, of three such samples on the Q-T interval of the electrocardiogram, stated in relation to the cardiac cycle length, made it possible to distinguish potencies related as 75: 100: 125. Aged and fresh samples of the same tincture were similarly tested.

The conditions for satisfactory clinical assay of digitalis are discussed, and a standard set outlined.

AUTHOR.

Van Dyke, H. B., and Li, R. C.: A Study of the Standardization of Digitalis. II. The Relationship Between Laboratory Methods of Assay and Potency as Determined by Experimental Cumulative Poisoning and Clinical Standardization. J. Clin. Investigation 14: 733, 1935.

Two samples of leaf of *Digitalis purpurea* were found to be equally potent in mammals (cats and dogs) but to differ significantly in potency as measured by assay in frogs. They were also compared by means of cumulation experiments in dogs and by a satisfactory method of clinical assay.

The cumulation experiments in dogs (Table III) and the clinical assays (Tables IV and V) were in agreement with the assays in mammals (Table II).

AUTHOR.

Fowler, W. M., Hurevitz, H. M., and Smith, Fred M.: Effect of Theophylline Ethylenediamine on Experimentally Induced Cardiac Infarction in the Dog. Arch. Int. Med. 56: 1242, 1936.

The experiments reported here have demonstrated that theophylline ethylenediamine promotes the development of the collateral circulation in experimentally induced cardiac infarction in the dog. The results justify the use of this preparation in the treatment of disease of the coronary arteries and acute coronary occlusion.

AUTHOR.

Dameshek, William, and Colmes, Abraham: The Effect of Drugs in the Production of Agranulocytosis, With Particular Reference to Amidopyrine Hypersensitivity. J. Clin. Investigation 15: 85, 1936.

In twelve cases of agranulocytosis, although many etiological factors seemed operative, the only constant one was that of a drug, usually amidopyrine, administered either alone or in combination. Of eight patients who recovered, four were selected for special study of possible hypersensitivity to drugs.

One patient reacted strikingly (within 90 minutes) to the oral administration of 0.6 gm. (10 grains) of amidopyrine with the resultant clinical and hematological manifestations of agranulocytosis. Two other patients developed moderate leucopenic and clinical reactions; the fourth patient, given 0.3 gm. (5 grains) of the drug, developed no symptoms. The skin reactions to various scratch tests, patch tests, passive transfer tests, and intradermal tests with the drug alone were essentially negative. However, intradermal tests with a mixture of the drug and blood serum were strongly positive in all three cases tried.

Two of three patients, shortly after the intradermal administration of amidopyrine solutions for skin testing, developed all of the clinical and hematological features of agranulocytosis. The total quantity of amidopyrine used in these tests did not exceed 10 mg. ($\frac{1}{6}$ grain).

Numerous reports demonstrate that the use of drugs, particularly of amidopyrine both alone and in combination, is an important cause of agranulocytosis. The widespread use of these drugs and the relatively few cases of the disease suggest an idiosyncrasy or hypersensitivity on the part of certain individuals.

The experimental observations present conclusive evidence of extreme hypersensitivity on the part of certain individuals to amidopyrine. The production of agranulocytosis following the intradermal introduction of only a few milligrams of the drug tends to disprove the theory that the drug must be oxidized in the gastrointestinal tract before it can become toxic.

The negative intradermal tests with an aqueous solution of amidopyrine as contrasted with the strongly positive tests with a "serumized" solution suggest a possible drug-protein linkage as the basis of the "allergic" or hypersensitive reaction.

The fundamental mechanism by which the bone marrow becomes affected and agranulocytosis results has not yet been demonstrated. These observations together with others suggest that certain drugs may cause suppression, "maturation arrest," of granulocyte production. In an individual who is hypersensitive, "allergic," to a given drug, a minute amount may initiate the disease.

AUTHOR.

Book Review

FAILURE OF THE CIRCULATION. By Tinsley Randolph Harrison. Baltimore, 1935, 396 pages, The Williams & Wilkins Company.

This book was written by one who, with several associates, has been actively engaged for over a decade in the clinical and experimental study of the mechanism of the failure of the circulation. The structure of the presentation consists in an introduction, five sections of discussion, and a summary. A selected bibliography and author and subject indexes are appended.

In the concise historical introduction, the author presents the early history of the knowledge of circulatory failure, bearing particularly on the concepts of "forward failure" and "backward failure" of the circulation (i.e., whether the early and primary derangement of the circulation depends on the inadequate blood supply to the tissues resulting from decreased cardiac output, or on the engorgement of blood behind the failing or diseased portion of the heart). After justified apologies the author introduces the terms and concepts of hypokinetic, hyperkinetic, and dyskinetic syndromes. Whether these terms as representing basic concepts are constructive or entirely justified may be debated. Of the three syndromes, the hyperkinetic and hypokinetic syndromes are discussed in a summary fashion, while the dyskinetic syndrome (congestive failure) represents the bulk of the volume. In this part the author analyzes in detail the experimental and clinical evidence for and against the forward and backward failure theories. He concludes that the forward failure theory is not acceptable, and presents evidence favoring the backward failure theory. In the succeeding chapters, the mechanism of a number of the important phenomena of the failure of the circulation is presented in a selective manner. The conclusions of some of the chapters are reached on the basis of the analysis of the literature, and of others on the basis of rich personal experience. The chapters on dyspnea and edema are particularly good. The discussions on the classification and measurements of dyspneas, the causes of dyspnea on exertion, the mechanism of orthopnea, paroxysmal dyspnea, and Cheyne-Stokes' respiration are stimulating and reveal valuable information with much originality. The numerous other manifestations of circulatory failure are treated concisely, rather in a clinical descriptive than in an analytical manner. The section on the therapeutic action of digitalis is excellent in describing the mechanism whereby digitalis produces improvement. There is in addition a short section on the failure of the coronary circulation.

The style of the book is simple and direct. There is, however, a lack of uniformity in the construction of the chapters. The book serves as an excellent demonstration of the methods and tools used in clinical sciences today. Clinical observations and descriptions are related to results of well-conceived experimental studies, though the ratio of the correlation varies widely in different chapters, depending primarily on whether or not the author has done work on the subject. In arrangement the book is a cross between a monographic presentation and a detailed textbook of specialties. It is a well-focused and excellent presentation of the subject in the light of personal experience and opinion by one who has pondered over the problems. The book is not for the use of the average physician interested in general medicine. Rather it is a reference book for those desiring to be, or considered as, experts in diseases of the heart and the circulation, and for all students who are interested in the functional approach and analysis of clinical phenomena.

S. W.

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COMPENSATION AND FAILURE OF THE RIGHT VENTRICLE*

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THE right ventricle is normally adapted for response to widely different volumes of venous return, but it is not accustomed to react against such great variations in arterial resistance as is the left. Under pathological conditions when the pulmonary resistance increases gradually as in pulmonary arteriosclerosis, mitral stenosis, etc., biological reactions occur which lead to hypertrophy of the chamber. When, however, pulmonary resistance is rather suddenly increased as happens, for example, through multiple embolism of pulmonary branches or massive embolism of the main vessel, the compensatory mechanisms held in reserve by the normal ventricle must be relied upon. As soon as the resistance offered exceeds the capacity for compensatory response, rapid failure of the right ventricle supervenes.

How large a physiological factor of safety the right ventricle possesses for meeting such emergencies can be evaluated by determining the greatest possible reduction in the pulmonary vascular bed before the supply of the left heart suffers and arterial pressures decrease. The results of earlier investigations summarized by R. Tigerstedt¹ indicate that more than one-half and often two-thirds of the pulmonary branches can be ligated in experimental animals before mean arterial pressure is reduced significantly. More recent experimental observations by Haggart and Walker² and Gibbon, Hopkinson, and Churchill³ have further shown that the lumen of the main pulmonary artery can be reduced approximately 60 per cent without reduction in arterial pressure.

While numerous studies upon the consequences of pulmonary obstruction are on record, no satisfactory analysis has yet been made of the compensatory mechanism whereby the right heart is able to carry on an adequate circulation despite great reduction in the pulmonary vascular bed and of the dynamic reactions responsible for the circulatory failure when obstruction exceeds a critical value. Records of mean

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systemic, mean pulmonary and venous pressures cannot advance our conceptions much beyond the time of Cohnheim; they at best give only an inkling of what might transpire. Minute volume determinations involving complex gasometric analyses actually yield no information that could not be supplied by an intelligent analysis of mean blood pressure tracings. Oneometric studies of the two ventricles do not permit differentiation between effects in the right and left ventricles, so essential in these conditions. In short, modern methods capable of elucidating the character of dynamic disturbances have so far not been used in a complete study of the question. Such incidental observations as have been made by modern methods (e.g., those of Wiggers¹¹ Straub,⁸ Katz, Ralli, and Cheer,⁵ and Wagner¹⁰), though indicative of what could be

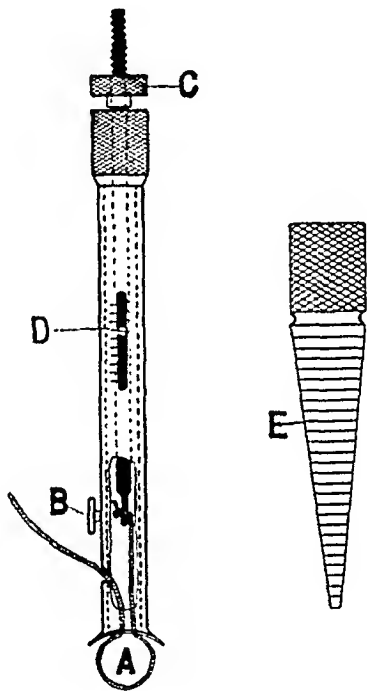


Fig. 1.

expected, were not primarily designed for a considered study of the questions at issue and moreover are not entirely in agreement.

Since the reactions of the right ventricle can be evaluated by optical registration of right ventricular pressures, and even slight impairment of left ventricular output can be judged by simultaneous registration of aortic pressure pulses, we employed these means of interpreting the effects due to graded compression of the pulmonary artery.

METHODS

Dogs were anesthetized by means of morphine and sodium barbital; the chest was opened and the heart exposed in the customary manner. The pulmonary artery was dissected sufficiently so that a stout ligature attached to a compressor could be passed around the vessel. The footplate of the compressor (Fig. 1) was placed upon the artery and the ligature fastened to the catch (B) so that a loose loop

(*A*) encircled the vessel. During the course of observations, this loop was progressively decreased in diameter—and the pulmonary artery with it—by tightening a screw (*C*) at the top of the compressor. A calibration on the moving screw thread (*D*) gave an arbitrary reading scale. At the end of an experiment the area of the loop as used at different readings of the scale was measured by means of a conical calibrated gauge (*E*), similar to a ring gauge used by jewelers. The area of the severed pulmonary artery was likewise measured by this gauge, and the diameter of the vessel walls was determined. By use of these data the arbitrary readings of the compressor could be given actual values.

During an experiment the vessel was compressed by this instrument in a graded fashion, 3 to 5 minutes being usually allowed between successive compressions for circulatory adjustments to the new conditions.

Pressure pulses from the right ventricle and aorta were simultaneously recorded by use of the Wiggers optical manometers, the customary technique of the laboratory being followed (Wiggers¹²). Records were taken between each additional compression. In some experiments, electrocardiograms (conventional Lead II) were taken in addition.

RESULTS

Segments of records illustrating typical effects of graded compression of the pulmonary artery are reproduced in Fig. 2.

Previous to their analysis it may be useful to review concisely the information that such curves are capable of supplying. The aortic pressure pulse (upper curve) gives direct information as to diastolic (*B*) and systolic (*C*) pressures in the aorta and their difference, which constitutes the pulse pressure. These are the pressure values one ordinarily determines by clinical methods. Variations in duration of the heart cycle (i.e., heart rate) and duration of left ventricular ejection (*B-D*) can be determined precisely with reference to the time abscissae below. The magnitude of the pulse pressure corresponds to the volume of systolic discharge provided drastic changes in peripheral resistance do not occur. The changing velocities of left ventricular ejection are mirrored in the contour of these pressure pulses (Wiggers and Katz¹⁴). Thus the rapid initial discharge of the left ventricle corresponds to the sharp rise (*B* to *C*), and reduced ejection toward the end of systole is responsible for the gradual decline of aortic pressure from the summit (*C*) to the incisura (*D*). Similar information regarding ejection of the left ventricle can be gained clinically by registration of the subclavian pulse.

The right ventricular pressure curve (lower) gives information regarding the changing behavior of the right ventricle. The pressure level at *A* represents the *initial* tension under which the ventricle starts its contraction. It gives important information as to the venous pressure level and the diastolic size of the right heart. Ejection begins at *B* and the summit reached at *C* normally corresponds to the pulmonary systolic pressure. The systole of the right ventricle (*A-D*) with respect to cycle length can be calculated.

In the successive records of Fig. 2, the degree of pulmonary compression is expressed as percentile reduction of the natural lumen, and

the durations of right ventricular systole are written below the curve. A glance at these segments shows that there is no measurable change either in the magnitude or in the contour of the aortic pressure curve—i.e., in left ventricular output—until segment *F*. Data from this and other experiments indicate that such complete compensation of the right ventricle obtains with compressions equal to 52, 70, 65, 41, 72, 49, 59 per cent (average, 58 per cent).

Up to this time significant changes have occurred in the right ventricular curve (lower). The maximum pressure (*C*) starts to increase at once and continues to mount in successive segments, the peak (*C*) moving gradually to the right. These changes signify that the right ventricle successfully overcomes increasing resistance to ejection by the development of a higher intraventricular pressure during systole.

Two different mechanisms occurring in sequence seem to be concerned in the production of such a response. A careful study of the segments in Fig. 2 and of similar records from other experiments consistently showed that the first increase in right ventricular tension is *not* associated with a rise of initial tension (*A*) nor with changes in duration of contraction. Beginning with segment *E*, however, the initial tension increases and with it a further marked augmentation of pressure and a prolongation of systole occurs. The transition point at which this change became noticeable occurred in various experiments when the degrees of pulmonary compression were 48, 43, 36, 24, 47, 41, 50, 46, 43, 48, 62 per cent (average, 45 per cent). Such results signify that the first compensatory increase in right ventricular pressure (up to segment *E*) is solely the result of an increased load in the pulmonary artery, but, as soon as the right ventricle through operation of this mechanism alone cannot empty itself to quite the normal extent, a small systolic remainder occurs. This, added to the normal inflow volume, acts to raise initial tension and slightly increases the diastolic size. As a result of these changes, the pressure development increases markedly, and systole is prolonged. These compensatory reactions produced through stretching of the ventricle have been found to be of great importance in adapting the left ventricle to great increase of aortic resistance (Wiggers,¹³ Wiggers and Katz,¹⁴ Katz, Ralli, and Cheer⁵). They have also been found to be of considerable importance in adjusting the output of the right ventricle to great increases of venous return (Wiggers¹¹). The small margin between the degree of pulmonary resistance, at which this mechanism is first invoked (segment *E*), and that at which the output of the left heart begins to suffer (segment *F*) suggests that this compensatory mechanism is of but limited value in overcoming augmented pulmonary resistance.

The records of Fig. 2 succeeding segment *F* show clearly the mechanism by which the ventricle fails in the majority of experiments. Despite the further elevation of right ventricular pressure, the systolic dis-

charge of both ventricles decreases; consequently blood accumulates in the right heart. The initial tension (*A*) therefore increases progressively; the right ventricle distends and venous pressures necessarily rise. In segment *G* we note that the gradients of the curves are no longer so steep and that the duration of systole decreases, confirming the interpretations of Feil and Katz² that this is early evidence of incipient myocardial fatigue. In segments *H* and *I*, despite further increase of initial tension (*A*); the pressure maximum (*C*) is much lower and

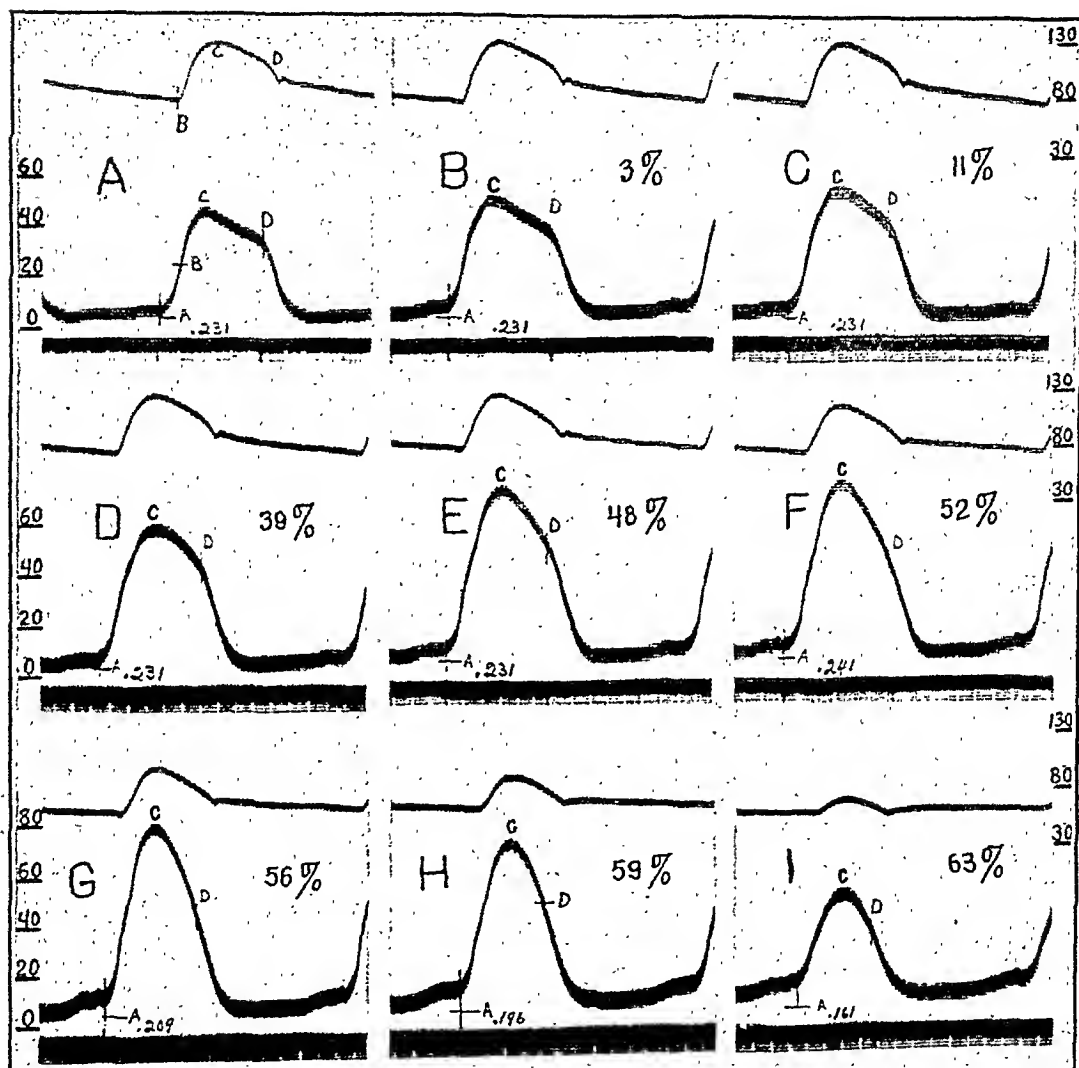


Fig. 2.

systole (*A-D*) is further shortened. This failure of the right ventricle to maintain a high systolic pressure (fatigue) is the immediate cause of the smaller delivery of blood to the left ventricle, its reduced output, and the decline of systolic and diastolic aortic pressures.

Our experiments indicate, furthermore, that these changing responses of the right ventricle are progressive with increasing degrees of pulmonary compression. They are progressive also in the sense that if compression be maintained for a considerable time at a dynamic stage represented by segment *F* for example, a subsequent set of changes

represented by segments *G*, *H*, and *I* is likely to supervene, and the animal may die as a result of hypodynamic action of the right ventricle.

The reasons for such prompt failure, which contrasts strikingly with the sustained compensatory reactions of the left ventricle as described in similar compressions of the systemic aorta by Katz, Ralli, and Cheer,⁵ are (1) the smaller bulk of right ventricular muscle and (2) the decrease in aortic pressure and coronary blood supply. In fact, when aortic pressures fall ever so little as in segment *F*, the right ventricle is required to work harder with a smaller volume flow through its coronaries. A vicious circle is thus established which can be broken only by prompt reduction of the high pulmonary resistance.

While this mechanism of cardiac failure predominated in our experiments, another mechanism was frequently found to supervene, in terminal stages. It was noted in some experiments that the heart slowed tremendously and in some instances stopped completely, after a dynamic stage represented by segment *H* had been reached. Since it was not abolished by vagus section an intrinsic cardiac mechanism was suspected. Electrocardiographic tracings indicate clearly that the sinus pacemaker failed and that A-V nodal or idioventricular centers maintained the beat. In some cases these also failed, and the heart just stopped. In other instances ventricular fibrillation supervened. Conduction disturbances were frequently noted as was evidenced by prolonged P-R intervals, periodic A-V block, and changes in the QRS complexes. Impairment of blood supply offers the best explanation for these phenomena.

DISCUSSION

Our studies upon the reactions of the right ventricle to graded increase in pulmonary resistance are of practical as well as of scientific interest.

In the first place, our observations confirm the impressions of most experimenters from the time of Cohnheim in 1889 to the present day, viz., that the circulatory failure following obstruction or compression of the pulmonary artery is due solely to fatigue and failure of the right ventricle. We were entirely unable to confirm the conclusions of Gibbon, Hopkinson, and Churchill³ that with certain favorable degrees of occlusion of the pulmonary artery—i.e., between 60 and 85 per cent—circulatory failure does not result “from a precipitate failure of an overloaded right heart but from a gradual withdrawal of blood from active circulation. . . . Death under these circumstances occurs as it does in hemorrhage or shock—not primarily from cardiac failure but from the effects of a reduced volume of circulating blood.”

A perusal of the experimental data submitted by these investigators makes it difficult to understand upon what facts such a conclusion was reached. Blood volume determinations are not reported and a fall of venous pressure—a sine qua non of shock and hemorrhage—is not described. Either some confusion existed between *cardiac minute output and volume of blood in the vascular system*, or it was not recognized

that reduced cardiac minute output can occur even with an excessive blood volume. In short, their report contains no single bit of evidence for the conclusions reached. The clinical histories of cases with pulmonary embolism in which death follows only after a lapse of hours with signs of progressive circulatory failure can easily be harmonized with progressive failure of a right ventricle. The rise of venous pressures coincident with such circulatory failure is also indicative of right ventricular fatigue but is not at all concordant with the shock hypothesis.

In the second place, our results emphasize that the right ventricle has only a limited power of response to drastic sudden increase in pulmonary resistance, and that fatigue and failure easily supervene when aortic pressure, and with it coronary flow, is suddenly reduced. When, in addition, some degree of anoxemia exists, as may happen in pneumonia for example, it is easy to understand why a circulatory crisis may be brought about through failure of the right ventricle even without auricular fibrillation. The possibility of doing harm by use of pressure-lowering drugs in every case with acute accentuation of the pulmonic second sound cannot be overemphasized and the possible value of pressor agents such as small doses of epinephrine, ephedrine, neosynephrine, etc., which incidentally are also cardiac stimulants, should be considered whenever increased pulmonary resistance is suspected to have occurred rather suddenly.

Finally, our experimental work stresses the futility of venesection in such cases. The right ventricle is able to respond to far greater elevation of initial tension than seen in our experiments before failure occurs, provided the pulmonary circuit is fully patent (Wiggers¹¹). Therefore, no reason exists for believing that the stretch encountered during diastole is a serious factor in the onset of fatigue, which seems to be due rather to the increased resistance encountered during systole, making right ventricular contraction more nearly isometric. On the contrary, lowering of initial tension by venesection would deprive the heart of a valuable mechanism for compensation. The physiological premises that appear to favor use of venesection in cardiac decompensation due to valvular lesions and primary failure of the left ventricle (Eyster¹) cannot apply to conditions in which the right ventricle is primarily strained.

The scientific aspects of our observations have a bearing upon the fundamental forces that govern altered contraction of a ventricle. Experimental observations have stressed the importance of initial tension and diastolic size as fundamental in compensatory reactions of the heart regardless of whether primary variation of rate, venous return or arterial resistance are involved (Wiggers^{12, 13}). Perhaps the importance that the load during contractions (of the right or left ventricle) plays has been insufficiently emphasized, despite various indications that it does affect the contraction process. Patterson, Piper, and Starling⁶ found that increasing the aortic resistance, the systolic discharge being

constant, tends to prolong ventricular contraction. Wiggers and Katz¹⁴ found only an abbreviation of systole until the diastolic size of the ventricles increased, in which case it was prolonged. They therefore believed that increased load per se tends to shorten the contraction. Wiggers¹² noted that immediately following aortic compression left intraventricular pressures mounted to higher summits for a few beats previous to rise of initial tension, the duration of contraction also being less. Katz, Ralli, and Cheer⁵ made a few observations upon the effects of abrupt compression of the pulmonary artery. They found, in addition to the immediate elevation of the pressure peak, an increased duration of systole and broadening of the curves before initial tension had increased, but observed, as we did with more graded compression, a further favorable effect when initial tension subsequently increased. Stella⁷ concluded from experiments on the perfused turtle heart that "the contractile stress set up in muscle at any moment is determined by its volume at that moment and by the time that has elapsed since the commencement of systole."

In the experiments now reported we observed that when the size of the artery is decreased roughly up to 40 per cent (segment *D*, Fig. 2), the pressure peak increases progressively without change in initial tension. The graded and persistent character of the response, far more than the transitory changes heretofore reported on mammalian hearts, supplies convincing evidence that the magnitude of the load after ventricular contraction has started affects the amplitude of contraction. In these experiments the changes in gradient, as could be expected, involve solely the part of the curve that comes during the ejection phase, and the duration of contraction remains unaffected. We are therefore led to question whether the slight abbreviation of left ventricular systole with increased resistance, previously reported from this laboratory,¹⁴ is after all a direct effect of the load. The possibility that it may be associated with improved coronary flow may be suggested. Prolongation of contractions (e.g., segment *D*) seems to be associated solely with rise of initial tension under the conditions of these experiments. This does not preclude a lengthening influence such as Katz, Ralli, and Cheer⁵ and also Stella⁷ noted when resistance was abruptly increased without rise of initial tension.

In formulating the laws that govern cardiac response, greater account must therefore be taken of the effect of load upon release of mechanical energy, oxygen consumption, and tendency to development of fatigue.

CONCLUSIONS

1. The reactions of the right ventricle to increasing gradual compression of the pulmonary artery were studied by simultaneous registrations of right intraventricular and aortic pressures by optical manometers.
2. Compensatory reactions which are sufficient to prevent changes in aortic pressure pulses occur up to the point where the pulmonary

compression equals about 58 per cent. They involve (a) primary reactions of the right ventricle to increased load and (b) secondary reactions due to increased initial tension and diastolic stretch of the right ventricle. Both increase the pressure maximum in the right ventricle, but the latter alone acts to prolong contraction. This pressure rise is sufficient to overcome the added pulmonary resistance, with the result that the supply of blood to the left ventricle does not suffer.

3. The normal transfer of blood to the left ventricle begins to diminish slightly while these compensatory mechanisms are still in operation, with the result that a slight decrease in aortic pressures occurs. The continued operation of the right ventricle under stretch combined with increased resistance leads readily to beginning failure, particularly when coronary blood flow is simultaneously reduced by lower arterial pressure. Similar changes follow still more rapidly when the degree of compression is increased further. The initial reduction in duration of contraction with slow pressure gradient presages onset of fatigue. The actual reduction in amplitude of the intraventricular pressure curves with rising initial tension establishes its existence.

4. No evidence was discovered, or has in our opinion been presented by others, that circulatory failure following obstruction of the pulmonary circuit has any other cause than fatigue of the right ventricle.

5. The clinical and academic importance of these observations is discussed. The importance of attempting to maintain an adequate arterial pressure and coronary flow in the avoidance of right ventricular fatigue, the possible harm from use of pressure-lowering drugs and the futility of venesection are stressed as points of clinical interest. The demonstration that intraventricular pressures can increase without rise of initial tension for considerable intervals of time as a result of increased load supports previous indications that changes in initial tension and diastolic size are not the only fundamental mechanisms that determine the release of energy during ventricular contraction.

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EXTRASYSTOLES OF CLINICAL SIGNIFICANCE*

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A GENERATION ago extrasystoles, or premature beats, were regarded as evidence of myocardial damage, and their recognition in a patient often led to the pronouncement of a gloomy prognosis. Gradually it was realized that they are frequently encountered in hearts that are otherwise normal, and, led largely by the teachings of Mackenzie, physicians learned to regard them as innocuous and to ignore them in the clinical evaluation of a case. Many attempts have been made, on the basis of statistical studies and of clinical analyses to determine their significance more accurately, and to discover whether particular kinds of extrasystoles have special meaning. At least 50 per cent of patients with extrasystoles have hearts that are normal, as far as can be determined, and the occurrence of extrasystoles in diseased hearts seems to follow no recognizable rules. It has been generally accepted that extrasystoles occurring in individuals with hearts that are otherwise normal are not portents of present or future heart disease and that in the presence of frank heart disease their appearance does not add to the gravity of the prognosis.

A common error has been in the evaluation of extrasystoles on the basis of mortality experience alone. Since a physiological disturbance may offer evidence of some derangement of the body without leading to death, it would seem worth while to pursue the question whether extrasystoles may ever offer evidence of myocardial damage, which need not be permanent or irreversible. If so, they gain in significance and may serve as useful aids in diagnosis and treatment.

Extrasystoles arise supposedly from an irritable focus in the auricular or ventricular myocardium. At times the cause seems quite clear. Thus extrasystoles induced by smoking, by coffee, or by the administration of salicylates¹ or of digitalis disappear when the offending agent is removed. Their occurrence under such circumstances indicates the reaction of the heart to a poison and calls for the removal of the toxic substance.

Less clear-cut is the mechanism of extrasystoles that occur in association with gallbladder disease, or with gastrointestinal disturbances, and that disappear following the correction of the abdominal condition. They may be toxic or reflex in origin. Reflex or neurogenic extrasystoles will not be further discussed at this time, for they are rarely

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signals of heart disease. However, in some instances, myocardial damage seems to sensitize the heart to respond in this manner to reflex mechanisms that may bombard normal hearts without giving rise to any irregularity.

Acute infectious diseases, acting in a manner similar to known chemical substances, can be the immediate cause of extrasystoles. When, with the onset of an acute febrile disease, extrasystoles suddenly appear in a patient whose heart has been regular, it is a sign that the heart has been injured by the infectious process. This does not necessarily indicate a serious prognosis or permanent damage to the heart. The following two cases illustrate such a chain of events.

A man twenty-three years old was taken ill with a sore throat followed by mild bronchopneumonia. On the fourth day of his illness one of his wrists became swollen, red, and tender. The following day his cardiac rhythm which had been completely regular became grossly irregular due to the occurrence of a great number of extrasystoles. This irregularity persisted a number of days, and, as it disappeared, a systolic murmur became audible at the apex. The fever lasted three weeks. The murmur persisted during convalescence.

A boy, aged fourteen years, had a coryza with fever for two days. On the third day he had a chill, and one of us was called to see him. He did not appear acutely ill, although his temperature was 105° F. The throat was red; the lungs were clear. The conjunctivae were injected. The heart was not enlarged; the heart sounds were of good quality; and there were no murmurs. The heart rate was 120, and there were many extrasystoles, which became more frequent when he sat up and breathed deeply. The fever persisted for five days. On the fourth day of his illness a fine macular rash appeared all over the body and faded in a few days. Reexamination a month later revealed a normal heart with a rate of 104. Slowing of the rate brought out rare extrasystoles both ventricular and nodal in type.

It seems clear that in these two cases the sudden appearance of extrasystolic arrhythmia during an acute infection indicated toxic or inflammatory myocardial involvement. In the first case, the subsequent development of a murmur gave further evidence that the heart was affected.

It is interesting to note that Mackenzie,² in his book, *The Study of the Pulse*, which appeared in 1902, stated that if extrasystoles appear in patients with lobar pneumonia before the crisis, the case will be fatal. However, he did not repeat this statement in any of his subsequent writings in which he always preached the innocuousness of extrasystoles. Gallavardin³ remarked that the appearance of extrasystoles in the acute myocarditis of infectious disease suggests a bad prognosis; Campbell⁴ believes that frequent extrasystoles occurring in patients with rheumatic heart disease indicate the presence of rheumatic infection or of a seriously overworked heart; Vaquez⁵ states that extrasystoles appearing suddenly during severe acute infectious disease should arouse suspicion of myocardial complications; Smith⁶ points out that extrasystoles may be one of the first manifestations of cardiac involvement during acute infectious diseases; Bass⁷ cites a number of con-

vincing cases in which this sequence of events took place; and finally Chagas⁸ found extrasystoles almost invariably in the cardiac form of trypanosomiasis.

The conclusion seems warranted that extrasystoles occurring at the onset and during the course of acute infectious disease indicate cardiac involvement, but not necessarily irreversible cardiac damage.

Auricular extrasystoles occurring in patients with mitral stenosis presage the appearance of auricular fibrillation.^{9, 10} Cowan and Ritchie¹¹ report that of thirty-two patients with auricular or nodal extrasystoles, seven developed auricular fibrillation, and ten died within a period of two years. Schwartz¹² has described patients with recurrent attacks of auricular fibrillation, in whom each paroxysm was preceded for several days by premature auricular beats, first coming on singly, then in groups. Some of these patients had mitral stenosis; others had hypertensive heart disease with early congestive heart failure. Duclos¹³ has reported the case of a man with hypertension and coronary artery disease who exhibited first auricular complexes of varying shape in the electrocardiogram, followed by auricular extrasystoles, and finally by auricular fibrillation.

Thus in patients with heart disease, auricular extrasystoles may presage the appearance of auricular fibrillation.

Multifocal extrasystoles, that is, extrasystoles arising from different foci in the auricles and ventricles are usually accompanied by severe myocardial disease. This has been well brought out by d'Irsay,¹⁴ who found that patients with multifocal extrasystoles have a higher mortality than those in whom premature beats are unifocal and that extrasystoles occurring in individuals with normal hearts are always unifocal. The latter observation has been confirmed by Peel.¹⁵ Gallavardin³ points out that frequent polymorphous extrasystoles, especially if they occur in short runs or if there is coupling, are a premonitory sign of ventricular fibrillation. We have observed one patient with multifocal auricular and ventricular extrasystoles and coronary artery disease who died in his sleep, without any premonitory symptoms, at a time when he seemed to be doing well. Not all multifocal extrasystoles indicate severe myocardial disease. Raimondi¹⁶ observed a twenty-two-year-old woman for a period of two and one-half years during which she received repeated refilling of an artificial pneumothorax. Following each filling multifocal extrasystoles appeared, which disappeared if the injected air was withdrawn. The severity of the arrhythmia paralleled the degree of filling. We have under observation a man, aged forty-one years, who has known of extrasystoles for seven years, but who has no symptoms past or present. The electrocardiogram five years ago showed auricular and ventricular extrasystoles. A recent electrocardiogram registered only auricular premature beats. There is slight slurring of the QRS complex in all leads; the R-T seg-

ments in Lead I and II have no isoelectric interval, and there is a Q-wave in Lead III. Physical examination is negative.

It has often been stated that extrasystoles appearing for the first time in middle-aged individuals should arouse the suspicion of coronary artery disease. This is too broad a generalization. At times, however, extrasystoles are closely linked with progressive disease of the coronary arteries. Recently Proger and his associates¹⁷ have shown that there is a group of patients with angina pectoris in whom extrasystoles appear shortly before the onset of pain, and disappear shortly after the cessation of the exercise that provokes the pain, and further that the abolition of the cardiac irregularity by the use of quinidine results in striking increase in capacity to work without pain. Bourne,¹⁸ who made a careful study of the effect of exercise on extrasystoles, found that individuals with normal hearts or with valvular disease exhibit a diminution in the number of extrasystoles during the deceleration period after exercise, but that in patients with coronary disease the extrasystoles are increased in number.

Laubry¹⁹ has pointed out that anginal attacks followed by extrasystoles should be regarded seriously. We have been impressed by the occasional apparently significant relationship between the occurrence of extrasystoles and of anginal seizures. We have observed a man, aged forty-eight years, who for eight months exhibited constant, frequent, unifocal ventricular extrasystoles and who experienced typical anginal pain on slight effort as well as at rest during this period of time. He finally had a coronary artery thrombosis, following which the heart became absolutely regular, and the anginal attacks no longer appeared at rest.

A woman, fifty-eight years old, had had diabetes mellitus for ten years and hypertension for seven years. Four years before she was seen, she had had an attack of severe precordial pain with radiation down the left arm, following which she was in bed for four weeks. She had had a number of minor attacks after that and two months previously again experienced a major seizure. Since then she had had daily attacks, frequently induced by eating. Examination revealed a nervous woman with flushed cheeks. The lungs were clear. Fluorosecopy revealed moderate enlargement of the left ventricle and slight dilatation of the aorta. The first heart sound was of fair quality; the aortic second sound was accentuated. There was a systolic murmur at the apex. The heart rate was 120, and there were many extrasystoles. The blood pressure was 210 systolic and 110 diastolic. The electrocardiogram revealed slurring of the R-wave in all leads, abnormal R-T transitions in Leads I and II, a prominent Q-wave in Lead III, and many multifocal ventricular extrasystoles. She was observed during a number of typical anginal seizures. During these the pulse rate remained rapid and irregular. Ten days later she suffered a slow coronary occlusion, and for the following ten days the rapid irregular rate persisted. The blood pressure dropped to 118/70. She then felt quite well for two weeks. There were no anginal attacks, and the pulse was regular. Then the anginal attacks as well as the extrasystoles returned, and two days later she developed another coronary artery thrombosis from which she died.

We have records of 974 patients with coronary artery sclerosis of whom 53, or 5.5 per cent, exhibited extrasystoles. Of these 9 were auricular, 42 ventricular, and 2 nodal. Of these 53 patients 11, or 21 per cent, have died, whereas of the 921 patients with coronary disease without this irregularity 96, or 10.4 per cent, have died.

Extrasystoles are often associated with coronary artery disease and under such circumstances may be indicative of rapidly progressive myocardial disease. Frequent extrasystoles in patients with coronary artery sclerosis, particularly if they follow thrombotic closure of a coronary artery, may be followed by ventricular tachycardia or fibrillation. It would seem wise, in such patients, to attempt to abolish the premature beats and to forestall the development of a fatal irregularity by the administration of quinidine sulphate. Five grains of the drug should be given three or four times a day.

Little thought has been given to the significance of extrasystoles occurring at rapid heart rates. It is well known that extrasystoles are encountered with diminishing frequency as the heart rate becomes more rapid and that at rates of 120 they are exceedingly rare.²⁰ Exercise, by accelerating the heart, usually abolishes the irregularity. For the same reason extrasystoles are unusual in febrile states and in hyperthyroidism. Hirshfelder²¹ and Smith⁶ claim that extrasystoles increasing with exercise indicate a weak myocardium.

Koppang²² encountered extrasystoles in only 17 of 1,000 electrocardiograms of 42 patients with diphtheria. The irregularity persisted at rapid heart rates and was regarded as evidence of myocarditis. Bohan²³ warns that extrasystoles occurring with heart rates above 100 are often indicative of myocardial disease. Esler and White,²⁴ who studied the prognostic significance of extrasystoles occurring at different heart rates, found that their appearance at increased rates does not increase the mortality, which is determined by the rapid heart rate alone.

While it may be true that in these cases the occurrence of extrasystoles does not add to the gravity of the prognosis, we believe that

TABLE I
DISTRIBUTION OF EXTRASYSTOLES ACCORDING TO HEART RATE

HEART RATE	AURICULAR EXTRASYSTOLES		VENTRICULAR EXTRASYSTOLES		NODAL EXTRASYSTOLES	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
30			1			
50-59	1	2				
60-69	3	6	6	4.8	2	40
70-79	14	28	16	12.8	2	40
80-89	11	22	35	28.0	1	20
90-99	9	18	33	26.4		
100-109	4	8	15	12.0		
110-119	6	12	11	8.8		
Over 120	4	6	9	7.2		
Totals	52		126		5	

their appearance at rapid heart rates is of real clinical significance. From this point of view we have analyzed the cases of extrasystolic arrhythmia that we have encountered during the past few years.

We have records of 183 patients exhibiting extrasystoles who were seen in office practice. In Table I these are arranged according to their heart rates.

Patients presenting themselves for cardiac examination as a rule are apprehensive, and their pulse rates are accelerated. This, undoubtedly accounts for the relatively rapid heart rates. Two-thirds of the cases of both auricular and ventricular extrasystoles occurred at heart rates between 70 and 100. An appreciable number occurred at rates above 110. An analysis of these last is presented in Table II.

TABLE II

CARDIAC LESIONS ASSOCIATED WITH EXTRASYSTOLES AT SLOW AND AT RAPID HEART RATES

DIAGNOSIS	AURICULAR EXTRASYSTOLES		VENTRICULAR EXTRASYSTOLES	
	HEART RATE BELOW 110	ABOVE 110	HEART RATE BELOW 110	ABOVE 110
Hypertension	8	2	28	2
Coronary artery sclerosis	3	1	21	8
Coronary artery thrombosis	3	2	10	3
Rheumatic valvular disease	8	1	7	2
Hyperthyroidism	0	1	0	1
Acute infection	1	1	1	1
Neurocirculatory asthenia	0	0	5	2
Auricular fibrillation	1	0	0	1
Normal heart	17	2	40	0
Totals	41	10	112	20

It is striking that with normal hearts no ventricular extrasystoles occurred at heart rates above 110 and that in only two instances did auricular extrasystoles occur at these rates (these were both in children).

The following is a brief description of the patients with *auricular* extrasystoles at heart rates above 110:

Two were women, aged sixty-five and forty-nine years, respectively, with essential hypertension and hearts that were only moderately enlarged and were well compensated. A forty-year-old man had numerous extrasystoles with unpleasant palpitation. Four years later with persistent auricular extrasystoles he developed typical angina pectoris. A man, aged forty-six years, had had a coronary thrombosis three months previously and when seen had active Graves' disease with a basal metabolic rate of plus 62 per cent and angina pectoris. He died suddenly four months after a successful subtotal thyroidectomy. A woman, aged thirty-six years, had far advanced rheumatic valvular disease and congestive heart failure, regular rhythm, and a rate of 120. At Mount Sinai Hospital we observed a similar case of a woman with mitral stenosis

and active rheumatic carditis, who had a heart rate of 120 with auricular extrasystoles. A man, aged forty-two years, had rheumatic mitral stenosis and insufficiency and angina pectoris. A man aged fifty-four years had active Graves' disease, enlarged heart, blood pressure of 140/60, and paroxysms of auricular fibrillation. A girl twelve years old in the third week of a bronchopneumonia had many extrasystoles at a heart rate of 130. There were two children with normal hearts, one aged four and one-half years, who had many extrasystoles when at rest with a heart rate of 80, and in whom the irregularity persisted when she cried and the rate rose to 120; and a girl aged sixteen years under observation for four years, who had persistent auricular extrasystoles with heart rates from 80 to 110.

Of the patients with *ventricular* extrasystoles with rapid heart rates, all but one of those who had hypertension or coronary artery disease were quite sick. One forty-nine-year-old man had had a coronary closure five days previously. A number had repeated anginal seizures at rest, and still others had gallop rhythm and congestive heart failure. Of those with rheumatic valvular disease, one had a far advanced valvular lesion with heart failure, the other had a fair cardiac reserve. The patient with Graves' disease had hypertension and an enlarged heart but did well after subtotal thyroidectomy. The case of the young boy with acute respiratory infection has been quoted previously. Finally there were two patients, a woman twenty-seven years old and one thirty-six years old, with anxiety neurosis and symptoms of neurocirculatory asthenia and with hearts that were organically normal. In each the heart rate was 110, and there were numerous extrasystoles.

A seventy-year-old man with myocardial fibrosis due to coronary artery sclerosis, with repeated attacks of paroxysmal dyspnea, on one occasion immediately after an intravenous injection of 2 c.c. of salyrgan developed a mild attack of paroxysmal dyspnea with a heart rate of 120 and many extrasystoles. At Mount Sinai Hospital we have seen not a few patients with myocardial failure and gallop rhythm following far advanced coronary artery disease who had persistent ventricular extrasystoles with heart rates above 110.

Thus the great majority of patients with either auricular or ventricular extrasystoles during rapid heart rates had definite, usually advanced, myocardial disease. No ventricular extrasystoles were encountered in individuals with normal cardiovascular systems and heart rates above 110, but two children had auricular extrasystoles at these rates. Two patients with ventricular premature beats at rates above 110 had no organic heart disease but had symptoms of neurocirculatory asthenia. This irregularity is apparently uncommon in neurocirculatory asthenia, for in 352 consecutive cases ventricular extrasystoles were encountered only seven times, and no auricular extrasystoles were seen. A woman

in the out-patient department with symptoms suggesting Graves' disease and a basal metabolic rate of plus 34 per cent had a heart rate of 112 and many nodal extrasystoles. She was admitted to the hospital for study. Here repeated metabolism readings were normal although the rapid pulse and extrasystoles persisted. Thus it was concluded that she had no hyperthyroidism but only neurocirculatory asthenia.

We have not encountered extrasystoles in patients with hyperthyroidism except in the presence of complicating heart disease. Thus of eighty-two successive cases of Graves' disease only two exhibited auricular and one ventricular extrasystoles. In these three cases the heart rates were above 110. One patient had had coronary artery thrombosis; another had essential hypertension with an enlarged heart; and the other had a large heart with attacks of paroxysmal auricular fibrillation.

Some authors have suggested that ventricular extrasystoles occurring in patients with auricular fibrillation add to the seriousness of the prognosis.^{9, 25} Our records of this combined irregularity are not sufficiently numerous to permit us to draw conclusions.

SUMMARY

Extrasystoles may offer valuable evidence of myocardial damage or strain, and their discovery should always lead to a careful cardiovascular examination and to an attempt to determine their cause. Commonly they result from tobacco, coffee, or digitalis intoxication. Their sudden appearance accompanying an acute infectious disease indicates that the heart muscle has been damaged by the toxins or virus of the disease. Auricular extrasystoles in patients with advanced heart disease, particularly with mitral stenosis, are usually forerunners of auricular fibrillation. Multifocal extrasystoles are usually accompanied by serious myocardial disease. Numerous extrasystoles occurring in patients with arteriosclerosis of the coronary arteries usually indicate a progressive vascular lesion. Short runs of extrasystoles or multifocal extrasystoles in such patients may be followed by sudden death, due presumably to ventricular fibrillation. In such cases the prophylactic use of quinidine sulphate is indicated. Extrasystoles occurring at heart rates above 110 are usually indicative of myocardial disease. Extrasystoles occurring in patients with active Graves' disease usually point to an accompanying cardiac lesion. Extrasystoles occurring without the above associations are without clinical significance.

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THE ENERGY METABOLISM OF THE HEART IN FAILURE AND THE INFLUENCE OF DRUGS UPON IT*

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THE most important characteristic of any machine doing work is its efficiency. The heart is a machine for transforming chemical potential energy into work in transporting blood around the circulatory system. The amount of energy it must expend in order to perform a given amount of work is of profound importance in the physiology, and especially in the pathological physiology, of the heart. To relate changes in the functional capacity of the heart to alterations in a physical property, its efficiency in converting energy into work, represents an advance in our conceptions of cardiac physiology. To be able to analyze and evaluate the effect of chemical agents upon the myocardium in terms of their effect upon the efficiency of the heart would seem to represent a further advance. In this investigation the energetics of heart muscle have been studied under various conditions. Some new light has been thrown on the changes occurring in cardiac failure in the heart-lung preparation, which changes are presumably similar to those in failure in the intact organism. The mechanism of the beneficial action of certain important cardiac drugs has been demonstrated, and a method has been developed which should be generally useful in evaluating drug action in terms of a physiological action.

METHODS

The energy liberated and work performed by the heart in a modified Knowlton and Starling¹ heart-lung preparation were measured. The oxygen consumption of the preparation was determined by the closed system spirometer method following Visser and Mulder.² The arrangement of apparatus (Fig. 1) is essentially that of the usual heart-lung preparation in an entirely closed system. The heart and lungs are completely isolated from the body of the dog and inclosed in an air-tight glass cylinder connected by large rubber tubing to an oxygen spirometer and the venous reservoir. This continuous air system affords automatic compensation for changes in the gas and fluid content of the lungs. The system is kept at constant temperature in a large bath adjusted to 37.5° C. A cardiometer, clamped rigidly in place in the glass chamber and connected to a large tambour, was used for recording ventricular volume.

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The apparatus was tested occasionally with a rubber lung. More than an entirely negligible decline of the oxygen spirometer tracing was never observed. The apparatus was also tested by measuring the oxygen consumption of the lungs following arrest of the heart.

The aortic blood pressure was recorded continuously by mercury manometer connected by side tube to the cannula in the brachiocephalic artery. The ventricular volume was measured continuously by the method used by Starling and Visseher,³ except that a rubber tambour system of small air volume but large diaphragm diameter (12 cm.) was substituted for the piston recorder. Only the maximum diastolic volume

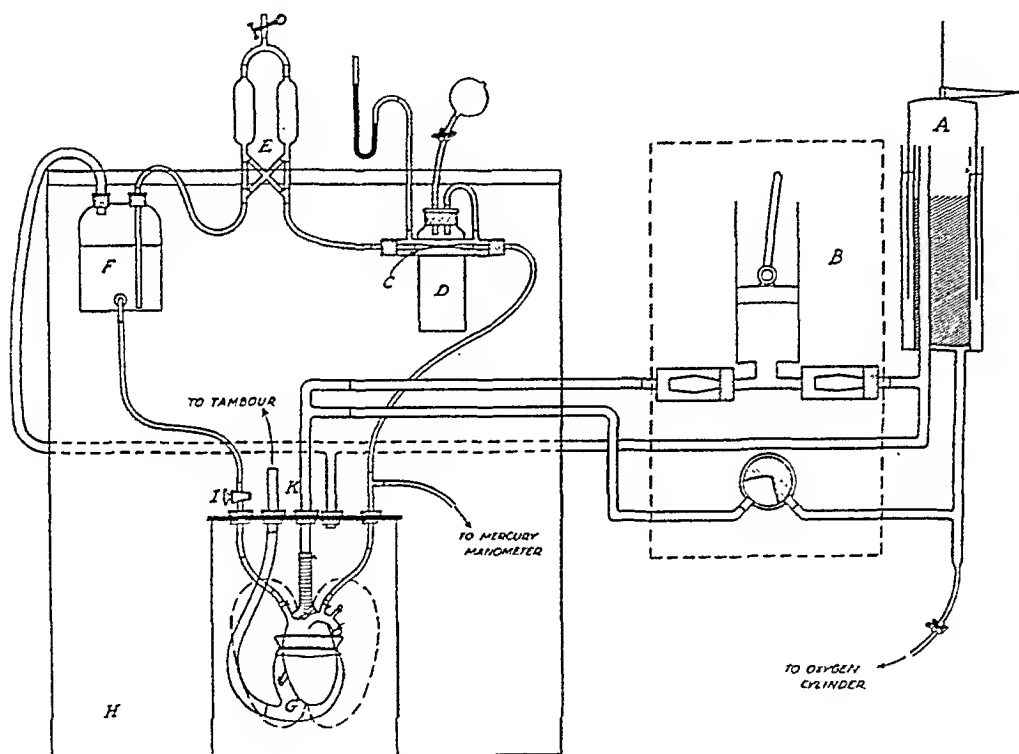


Fig. 1.—A, oxygen spirometer; B, respiration pump; C, artificial resistance; D, pressure bottle; E, Stromuhr; F, venous reservoir; G, cardiometer; H, constant temperature bath; I, stopcock for adjustment of venous return; K, tracheal cannula.

is considered in these studies, and this is the quantity most accurately recorded with the system used because the filling of the ventricle is slower and therefore more faithfully recorded than the ejection. In the latter there is considerable overthrow because of the inertia of the system. The inertia is less with the tambour than with the piston system. The calibration of the volume-recording system was performed after each experiment with the heart in the cardiometer. This is absolutely essential since the volume of air in the system determines the sensitivity of the device.

Oxygen consumption, arterial pressure, and ventricular volume were continuously recorded while rate and volume output were determined

at frequent intervals. The ventricular volume was controlled, when desired, by adjustment of the venous return.

Unless otherwise indicated, our figures for oxygen consumption are corrected for lung metabolism by subtracting 20 per cent of the initial consumption. This correction is admittedly rough, but, since relative rather than absolute values for efficiency are employed in whatever conclusions are drawn, no error should result. Total energy liberation is estimated on a basis of 5 calories per cubic centimeter of oxygen at standard conditions of temperature and pressure. Again, since we are interested in changes in oxygen consumption and efficiency rather than in absolute values, the exact value of the calorific equivalent of oxygen would be of no importance unless large changes in R. Q. occurred. We assume that there were no such changes.

The external or systemic work of the preparation is calculated from the expression, $W = 1.35 PV + 1.06 \frac{V}{2g} \left(\frac{8v}{3A} \right)^2$, where W is the systemic work done by the heart in gram-centimeters per minute, P is the mean arterial pressure in millimeters of mercury, V the volume output in cubic centimeters per minute, v the output in cubic centimeters per second, A the cross-section area of the cannula in square centimeters, and g the acceleration of gravity.

The external or systemic efficiency is the ratio of the external work to the energy equivalent of the oxygen consumption. It does not necessarily reflect changes in the condition of the muscle since the external efficiency may be affected by changes in the pulmonary and coronary circulations. The significance of changes in external efficiency must, therefore, be evaluated with some caution. If changes are small, conclusions regarding variations in the condition of the muscle may not be justified. Frequently, however, the changes observed are so large and the effects of the experimental conditions on the coronary and pulmonary vessels so well established that definite conclusions of fundamental significance for the cardiac muscle fiber may be drawn. Only such changes are here considered.

A. THE CHARACTERISTICS OF THE FRESH HEART

The description of the potential metabolic activity and mechanical performance of a heart at any instant involves a complex series of relationships. As the "physiological condition" of the heart changes under physical or chemical influences, a whole set of characteristic relations change, frequently rather rapidly. Since in the nearly normal or fresh heart a given condition can be maintained long enough for thorough investigation of one or several relations, we are able to arrive at a fairly complete description of its working properties. Our present knowledge of those properties and relations quantitatively characteristic for each heart includes average values for oxygen consumption and efficiency, and

various relationships between fiber length, work, total energy liberation, efficiency, temperature, and rate.

The average oxygen consumption of the frog heart has been estimated at 1.7 e.e. per gram of heart per hour at 18° C. by Weizsäcker⁴ and 1.0 e.e. at 13° C. by Clark and White.⁵ In the mammalian heart, values of 2 to 5 e.e. in cats and rabbits were obtained by Rohde.⁶ In the dog Evans⁷ found from 3.5 to 6 e.e. Clark and White have shown that if in the myothermic measurements of the initial heat liberated by the beating frog's heart, reported by Fischer,⁸ it is assumed that the total energy is 2.1 times the initial energy liberated, values are obtained consistent with the oxygen consumption measurements.

The maximum efficiency reported by Weizsäcker⁹ is 36 per cent, but this value is too high as he used 3.5 calories as the equivalent of 1 e.e. of oxygen. Clark's¹⁰ highest value for frog and turtle auricles is 20 per cent. His average value for the theoretical maximum efficiency is 40 per cent. The efficiencies estimated by Fischer are in fair agreement. In the mammalian heart the maximum efficiencies found by Rohde¹¹ were from 25 to 30 per cent. In dog heart-lung preparations perfused with blood the maximum efficiencies obtained by Evans and Matsuoka¹² were about 20 per cent.

The work, total energy liberation, and efficiency of the heart vary within wide limits depending on the physical conditions under which it works. Rohde⁶ observed parallel variations in the work and oxygen consumption of the hearts of cats and rabbits, and showed¹¹ that work, oxygen consumption and efficiency increased with the initial filling of the ventricle. In normal hearts he was able, under restricted conditions, to demonstrate a parallelism between the oxygen consumption and the product of rate and isometric pulse pressure. In the frog heart the dependence of work and oxygen consumption upon the initial filling was noted by Weizsäcker.

Since the heart is elastic and distensible, it was necessary to determine whether the increased contractile energy is due to increased initial length or increased initial tension. Blix¹³ and Hill¹⁴ concluded that for skeletal muscle, initial length determined energy liberation over a certain range of lengths since considerable changes in contractile energy, heat production and initial length occur with only slight changes in initial tension. The dependence of the work of the heart upon initial fiber length was demonstrated by Patterson, Piper, and Starling,¹⁵ who, in heart-lung preparations, showed that the heart responded to increased arterial resistance or venous inflow with an increase in diastolic volume and that, under certain experimental conditions, this adjustment was made, not with an increased, but with a decreased initial tension. These experiments also indicate the necessity of direct measurement of the diastolic volume since reliance cannot be placed upon the filling pressure alone as its determinant. Evans and Matsuoka¹² found that the oxygen

consumption increased with the work of the heart but could demonstrate only a rough correlation between the diastolic volume and the total energy liberation on account of an inadequate method of measuring ventricular volume. Using improved methods, Starling and Visseher³ showed for the first time that under widely varied conditions, including spontaneous failure, the oxygen consumption of the mammalian heart is an approximately linear function of the diastolic volume as long as rate, temperature, and chemical environment remain constant. This has been confirmed for the normal mammalian heart by Hemingway and Fee¹⁶ and for the normal cold-blooded heart by Clark and White,^{5, 10} Eismayer and Quincke,¹⁷ and Decherd and Visseher.¹⁸ Stella¹⁹ has submitted evidence to show that in the turtle heart the oxygen consumption and work increase with arterial resistance at constant diastolic volume. This relation was not confirmed by Decherd and Visseher.

It is generally agreed that within physiological limits the mechanical efficiency of cardiac muscle increases with the work of the heart (Weizsäcker,⁹ Rohde,¹¹ Evans and Matsuoka,¹² Starling and Visseher,³ Rühl²⁰). Gremels²¹ found, however, that the efficiency did not increase when increases in work were due to aortic pressure changes. An analysis of his protocols shows that this effect was associated with spontaneous failure during the time required for the measurements.

When the load imposed on the heart exceeds optimal limits, the heart continues to dilate (Patterson, Piper, and Starling,¹⁵ Starling and Visseher³), the oxygen consumption continues to rise with increased initial fiber length (Starling and Visseher) and with increased load (Evans and Matsuoka) while the work output of the heart falls (Patterson, Piper, and Starling, Starling and Visseher, Evans and Matsuoka). The same response to excessive loading is found in the turtle heart (Decherd and Visseher¹⁸). It has recently been shown (Smith²²) that the behavior of skeletal muscle is entirely consistent with these findings when the total metabolism, resting plus activity, is taken into account.

The energy metabolism of the heart is modified by changes in rate. In the frog heart Weizsäcker⁴ and Clark and White,⁵ using constant filling pressures, which probably kept initial tension constant except at high rates, found that for moderate rates the excess oxygen consumption above the resting level per beat is approximately constant. Their finding of a decreased excess oxygen consumption per beat at higher rates is probably due to a diastolic period too short to permit equilibrium with the filling conditions. Hence at higher rates the diastolic ventricular volume must have been reduced. The decrease in the volume output per beat at the higher rates also indicates a decreased initial fiber length. In the heart-lung preparation when the diastolic volume is kept constant, an increase in rate is accompanied by a less than proportional increase in the total oxygen consumption (Starling and Visseher). This is in agreement with the work on the cold-blooded heart for moderate rates.

If the work of the heart is kept constant, a decrease in rate is associated with an increased efficiency (Starling and Visseher).

Under varying conditions the work of the heart is limited by several factors. In heart-lung preparations in good condition the work output is limited by the pericardium (Evans and Matsuoka¹²). When this is removed, further loading increases the work of the heart until a maximum is reached beyond which the work of the heart falls off. The diastolic volume and oxygen consumption continue to increase, however, while the efficiency drops (Starling and Visseher,³ Decherd and Visseher¹⁸). It is probably true that under pathological conditions the work of the heart may be limited by the oxygen supply to the muscle fiber, but this is certainly not the case when a normal heart is excessively loaded.

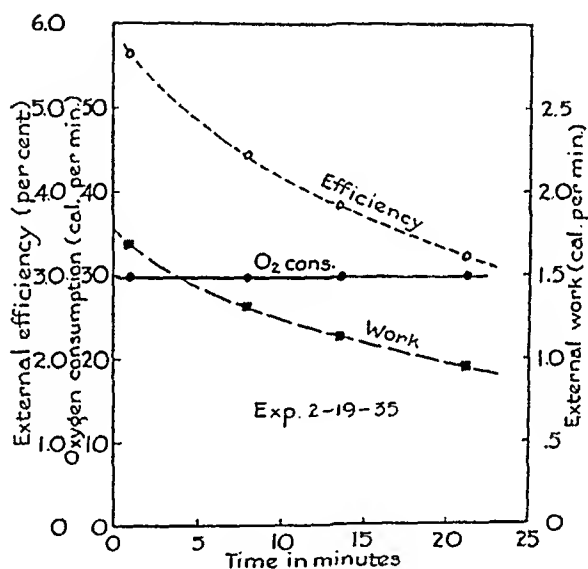


Fig. 2.—Spontaneous failure at constant external diastolic volume.

B. SPONTANEOUS FAILURE OF THE HEART

Failure of the heart is characterized by a decrease in capacity for doing work at a given diastolic volume (Starling²³). This might be due to a falling off of total energy liberation, a decrease in efficiency, or both. In cold-blooded hearts, perfused with balanced ion solutions, at constant initial tension, Bodenheimer²⁴ found a parallel decrease of oxygen consumption and the product of rate times isometric pulse pressure in spontaneous failure, and Clark and White,^{25, 26} and Eismayer and Quincke²⁷ observed a decreased oxygen consumption as well as a decreased work output. Under the same conditions except for the presence of serum in the perfusion fluid, Clark and White found that failure in the frog's auricle was due entirely to efficiency loss. Similarly, Decherd and Visseher,²⁸ who perfused turtle ventricles with a mixture of blood and Ringer's fluid, found that in failure work decreased markedly at constant diastolic volume and oxygen consumption.

In mammalian hearts Rohde^{6, 11} and Rühl²⁰ noted a decrease in work and in oxygen consumption, a rise in initial tension, and the development of cardiac edema. Evans and Matsuoka¹² and Gremels²¹ found that spontaneous failure was due to diminished efficiency with increased oxygen consumption. Daly and Thorpe,³⁰ who used the method of Barcroft and Dixon³¹ with a heart-oxygenator preparation, observed de-

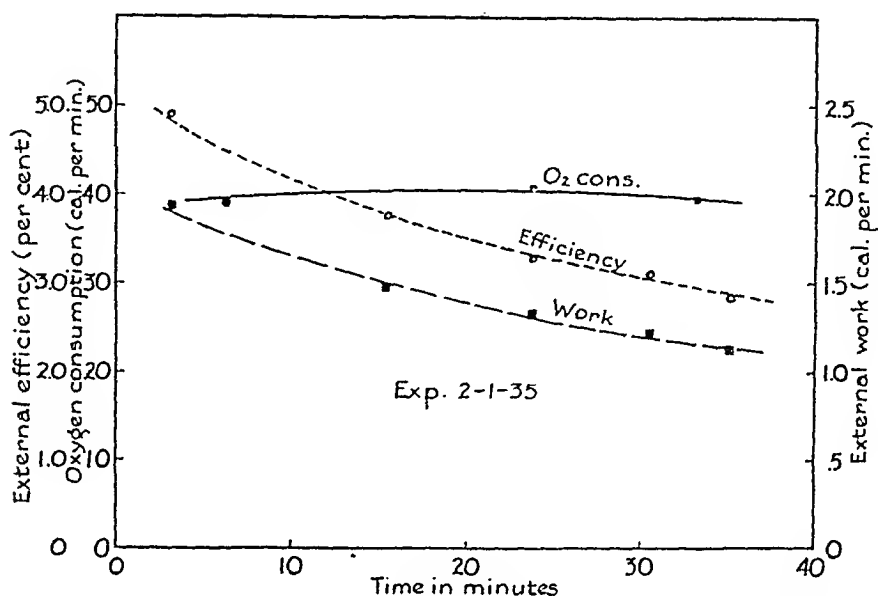


Fig. 3.—Spontaneous failure at constant external diastolic volume.

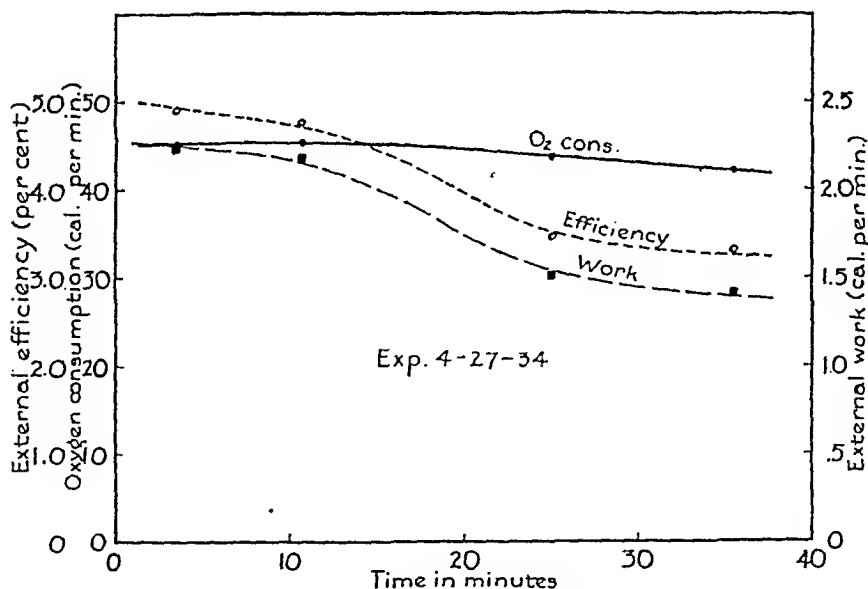


Fig. 4.—Spontaneous failure at constant external diastolic volume.

creased efficiencies in two experiments on spontaneous failure. The oxygen consumption increased in one experiment and decreased in the other although there seemed to be no dilatation in either case. According to Starling and Visser, the linear relation between oxygen consumption and diastolic volume was constant during the course of failure in their experiments.

Our methods of measuring oxygen consumption made it possible to study failure under a greater range of conditions than did Starling and Visser, who were forced to discard experiments showing any trace of pulmonary edema. At the same time the inaccuracies of Rühl's arterio-venous oxygen difference method were avoided. The course of failure

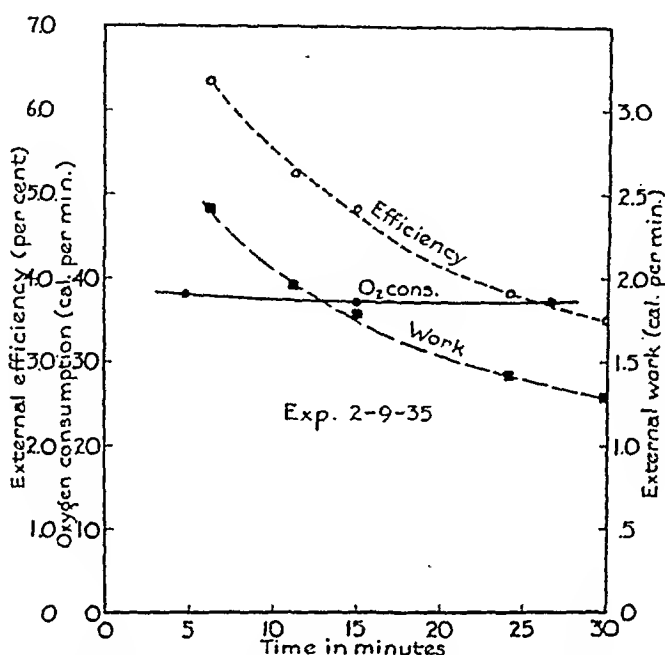


Fig. 5.—Spontaneous failure at constant external diastolic volume.

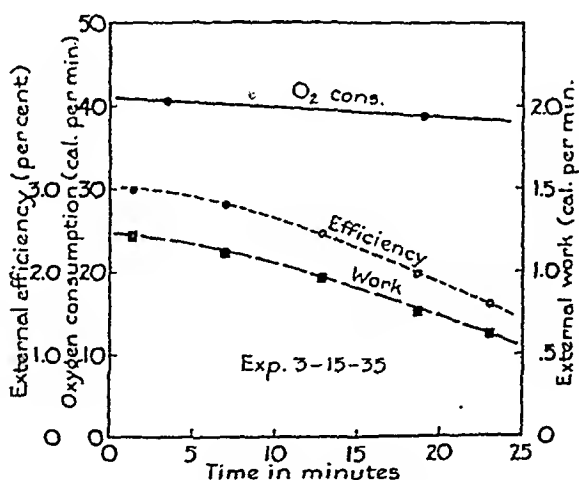


Fig. 6.—Spontaneous failure at constant external diastolic volume.

in nine hearts in which the external diastolic volume was kept constant by adjustment of the venous return is shown in Figs. 2, 3, 4, 5, 6, 7, 8, 10 and 11. It will be seen that in most cases loss of efficiency was almost entirely responsible for the decrease in working capacity. In two other experiments, not suitable for graphic presentation because of incomplete volume control or excessively rapid failure, the oxygen consumption for

a given external diastolic volume decreased. In the experiment of April 6, 1934, the oxygen consumption decreased 30 per cent in sixty-five minutes. The control of the diastolic volume was uncertain. In the experiment of Feb. 9, 1935, following a period of failure due to loss of efficiency alone, the oxygen consumption dropped 14 per cent in eleven minutes at constant external diastolic volume.

However, the demonstration that the oxygen consumption in failure

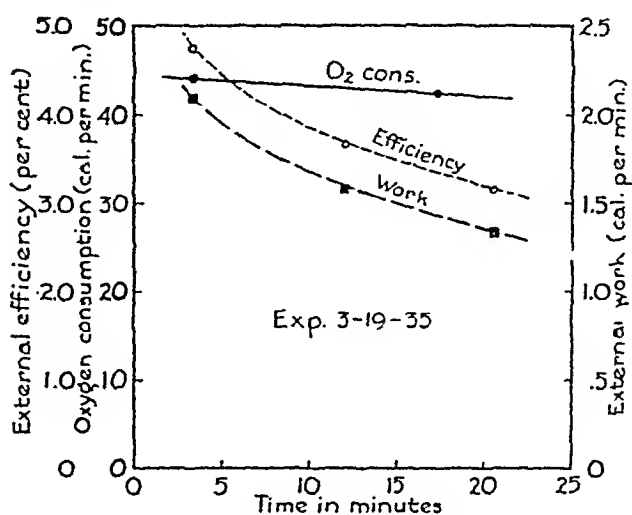


Fig. 7.—Spontaneous failure at constant external diastolic volume.

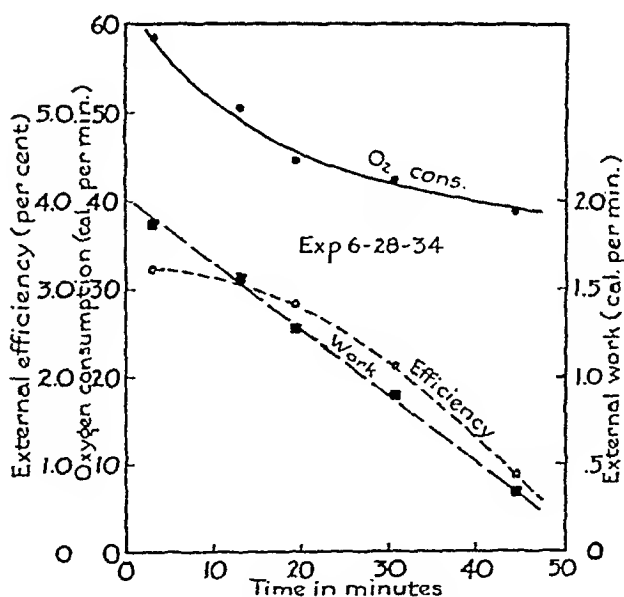


Fig. 8.—Spontaneous failure at constant external diastolic volume.

may decrease at a given diastolic volume, as measured by a cardiometer, does not prove that the oxygen consumption is not a function of fiber length. Changes in external diastolic volume reflect accurately changes in the mean diastolic volume and mean fiber length only if the volume of the myocardium itself remains constant. This factor must not be neglected, for, according to Rühl,²⁹ edema of the heart is the fundamental change in spontaneous failure.

An attempt has been made to estimate the effect of the hydration of the heart, which sometimes occurs in these experiments, on the mean diastolic volume when the external diastolic volume is maintained constant. A buret partly filled with water was connected to an air chamber in connection with the rubber tubing between the cardiometer and the recording tambour. A reference point corresponding to the volume of the myocardium was obtained by shutting off the venous return, cutting out the arterial resistance, clamping off the arterial tubing, and then drawing blood from the heart by means of a syringe connected to a side tube in the manometer tubing until it was no longer possible to reduce the pressure in the cardiometer system; the pressure was then adjusted to correspond to a reference line on the kymograph paper by adjustment of the water level in the buret, which was read. Successive readings made in this way indicate the change in the volume of the myocardium. The hydration during an experiment may amount to 20 c.c. per 100 grams of final ventricular weight (Fig. 9).

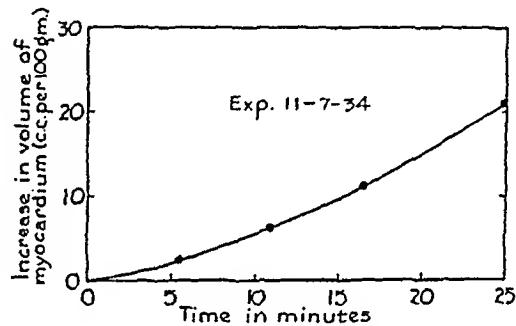


Fig. 9.—Hydration of the heart in spontaneous failure.

This degree of hydration will explain a considerable decrease in oxygen consumption at constant external diastolic volume. The most striking decrease observed by us was 19.6 calories per minute in the experiment of June 28, 1934 (Fig. 8). As the dog weighed 12 kg., the final weight of the heart was probably about 90 gm. (estimated from experiments in which the heart was weighed). Hydration, at 20 c.c. per 100 gm., would cause the volume of the myocardium itself to increase 18 c.c. in this preparation; and since the external diastolic volume was kept constant, the internal diastolic volume would decrease 18 c.c. and the mean diastolic volume would be reduced by 9 c.c. Since the metabolism of this preparation was very high, we have used the highest value of Starling and Visscher, 2 calories per minute per cubic centimeter (their Fig. 6), in estimating the reduction in oxygen consumption corresponding to this change in mean diastolic volume. This calculation gives $9 \times 2 = 18$ calories per minute, which substantially accounts for the observed decrease of 19.6 calories per minute.

While we have demonstrated that, under conditions favoring pulmonary and cardiac edema, the oxygen consumption of the spontaneously

failing heart may decrease at a constant external diastolic volume, we have no reason to believe that the total energy liberation decreases at constant fiber length. If, however, edema of the heart is so severe that the oxygen supply to the fibers becomes inadequate, it is to be expected that the oxygen consumption might decrease even at constant fiber length. This seems to be what may have happened in some of the experiments of Rühl.

C. THE INFLUENCE OF CHEMICAL FACTORS AUGMENTING FAILURE

Rühl²⁹ found that in failure due to histamine the oxygen consumption is decreased in spite of marked cardiac dilatation, as indicated by the rise in intra-auricular pressure. Since our experiments on spontaneous failure are at variance with those of Rühl, it seemed desirable to repeat his experiments on histamine insufficiency. In our experiments (Table I), in spite of some dilatation due to incomplete volume control, the oxygen consumption decreased, and this decrease cannot be fully accounted for by the change in rate. However, the effect lasts only five or six minutes and is followed by virtual recovery of normal oxygen consumption. This was apparently not observed by Rühl. The results of Rühl on spontaneous failure are probably due to the marked hydration he states that he obtained rather than to experimental errors, large as those may have been.

TABLE I
EFFECT OF HISTAMINE ON ENERGY EXCHANGES IN THE HEART

EXPERIMENT	DOSAGE		RATE	DIAS- TOLIC VOLUME (C.C.)	OXYGEN CONS. (CAL./ MIN.)	VOLUME OUTPUT (C.C./ MIN.)	EFFI- CIENCY PER CENT
6/4/35	0.002 gm.	Control	148	x	34.7	517	4.70
		After II	124*	x+30	22.4	307	3.93
6/5/35	0.0005 gm.	Control	136	x	21.0	446	6.94
		After II	115	x+6	10.6	182	5.07

*Irregular.

The barbiturates, numal, somnifen, and pernocton, as well as avertin, produce, according to Rühl,²⁰ failure entirely analogous to his histamine effects. Since this type of failure occurs spontaneously in his preparations, the experiments do not seem to be well controlled. Although we have not adequately studied other types of barbiturate failure, we find that failure produced by sodium amytal in small doses is entirely due to loss of efficiency (Table II). The effect occurs two or three minutes after injection and cannot be due to spontaneous failure.

The injection of parathyroid extract in suitable doses into the circulation of heart-lung preparations is followed by an increase in rate, a slight decrease in diastolic volume and a definite increase in the oxygen consumption rate. As the volume output is diminished or unchanged, the efficiency decreases (Table III). The oxygen consumption values

TABLE II

EXPERIMENT OF APRIL 4, 1935

EFFECT OF 0.020 GM. SODIUM AMYTAL ON ENERGY EXCHANGES IN THE HEART AT CONSTANT EXTERNAL DIASTOLIC VOLUME

OXYGEN CONS. (CAL./MIN.)		VOLUME OUTPUT (C.C./MIN.)		EFFICIENCY PER CENT		PER CENT DE- CREASE IN EFFICIENCY
CONTROL	AFTER S. A.	CONTROL	AFTER S. A.	CONTROL	AFTER S. A.	
24.7	25.0	667	429	8.97	5.18	42

of Table III are not corrected for lung metabolism. The increases in oxygen consumption cannot be explained by the rate changes. As the

TABLE III

EFFECT OF PARATHORMONE ON THE ENERGY METABOLISM OF THE HEART

EXPERI- MENT	DOSAGE		RATE	OXYGEN CONS. (CAL./MIN.)	VOLUME OUTPUT (C.C./MIN.)	EFFI- CIENCY PER CENT	PER CENT DECREASE IN EFFI- CIENCY
1/27/33	20 U.	Control	135	39.4	375	3.52	
		After P	138	44.0	366	3.06	12.9
1/27/33	20 U.	Control	140	41.5	385	3.44	
		After P	144	45.0	375	3.00	10.0*†
1/28/33	40 U.	Control	116	60.1	333	1.94	
		After P	136	67.5	333	1.72	11.2
2/21/33	20 U.	Control	88 (x2)	78.5	500	2.43	
		After P	98 (x2)	86.8	441	1.92	21.0†
2/27/33	20 U.	Control		77.0	667	3.38	
		After P		83.8	667	3.12	7.8*†
2/ 2/33	20 U.	Control	100 (x2)	36.8	423	4.15	
		After P	111 (x2)	35.9	308	3.01	27.5†
3/28/33	20 U.	Control	112	53.6	375	2.28	
		After P	128	73.3	349	1.54	32.5*
3/27/33	20 U.	Control	112	38.3	500	4.35	
		After P	118	42.3	500	3.95	9.2*

*After CaCl_2 .

†Irregular heart.

decrease in diastolic volume is transient, the initial fiber length during the experimental period may be assumed to be hardly different from the control. It, therefore, seems likely that parathyroid extract produces an increase in total energy liberation at a given fiber length independently of the rate changes.

Failure due to cardiac drugs may be produced by certain reputed "cardiac tonics" while others apparently exert no direct action on the heart at all. In a few experiments it was found that homocamphin was without effect, metrazol produced either no effect or a slight one due to an increase in rate, and myorgal and coramine both caused dilatation with an unchanged or diminished volume output and decreased efficiency. Most of the experiments on coramine were performed on irregular hearts following injection of drugs of the digitalis series, but two (Table IV), in untreated and slightly hypodynamic hearts, show clearly the metabolic effects of the drug. The decrease in the work output is en-

tirely due to loss of efficiency. This drug cannot be looked upon as a cardiac tonic, which it is claimed to be, since in doses that produce any effect at all there is loss in cardiac efficiency.

TABLE IV

EXPERIMENT OF MAY 17, 1935

EFFECT OF 0.25 C.C. CORAMINE (25 PER CENT SOLUTION) ON ENERGY EXCHANGES IN THE HEART

DILATATION DUE TO C. C.C.	OXYGEN CONS. (CAL./MIN.)		VOLUME OUTPUT (C.C./MIN.)		EFFICIENCY PER CENT	
	CONTROL	AFTER C.	CONTROL	AFTER C.	CONTROL	AFTER C.
3.0	37.5	40.2	500	460	4.01	3.40
2.5	36.0	37.9	558	548	4.85	4.52

D. PHYSIOLOGICAL ANALYSIS OF CARDIAC "TONICS"

In recovery from cardiac failure the heart's capacity for doing work at a given diastolic volume is increased. This increase is the result of changes in total energy liberation and mechanical efficiency. When recovery is due to the action of chemical substances, the efficiency changes cannot be predicted from the external diastolic ventricular volume alterations and the work of the heart, as has been assumed by those (Bodo³² and others) who have not attached sufficient significance to the statement of Starling and Visseher that the oxygen consumption is a function of diastolic volume when the chemical environment of the muscle fiber as well as certain other variables are maintained constant. It will be seen that the marked cardiac actions of adrenalin, calcium, and the glucosides of the digitalis series are associated with changes in total energy liberation, as well as efficiency, at constant external diastolic volume.

Adrenalin increases the oxygen consumption of the heart at a given diastolic volume independently of frequency changes. Rohde and Ogawa³³ found that the increase in oxygen consumption due to adrenalin was proportional to the change in the isometric pulse pressure-pulse rate product. In the heart-lung preparation Evans and Ogawa³⁴ observed that the increased respiratory metabolism is roughly proportional to the increase in rate. Starling and Visseher³ stated briefly that adrenalin increases the oxygen consumption at a given fiber length. Gremels,²¹ using the method of Starling and Visseher, found a marked increase in oxygen consumption due to adrenalin, only a small fraction of which can be explained by the minimal rate change. Since the diastolic volume must have decreased in his experiments, the increased total energy liberation at a given fiber length is certain. The efficiency decreased inasmuch as the work output was not significantly changed. From the evidence at hand it appears that if the diastolic volume is uncontrolled, adrenalin will not increase the efficiency of the heart unless it is so weakened that its output before adrenalin injection is very low at a con-

siderable filling pressure. A measure of cardiac action independent of filling conditions may be obtained by keeping the diastolic volume constant by adjustment of the venous return. Studies of efficiency changes produced by adrenalin under these conditions are lacking.

The influence of calcium ions on the oxygen consumption of the frog's heart has been studied by Clark and White,^{25, 26} who found that, with increasing calcium ion concentration, the mechanical response and the oxygen consumption both rise. Eismayer and Quineke³⁵ reported that calcium lack reduced the oxygen consumption but increased the efficiency of the frog's ventricle. One would expect from the work of Clark and White²⁵ that the efficiency would be reduced by lowered calcium ion concentrations.

In the heart-lung preparation, when the venous return is not controlled, administration of calcium markedly increases the output and efficiency of hypodynamic hearts but has little effect on these variables in fresh hearts (Peters, Rea, and Vischer³⁶). When the external diastolic ventricular volume is maintained constant, oxygen consumption and efficiency are both increased. The average percentage increase in efficiency (external) of 75 per cent must be due to a definite increase in the efficiency of the muscle (Table V).

The metabolic effects of glucosides of the digitalis series on the heart have received considerable attention, but the results are conflicting, partly because of inadequate methods and partly because of failure to

TABLE V

EFFECT OF CALCIUM ON ENERGY LIBERATION AND EFFICIENCY OF HYPODYNAMIC HEART AT APPROXIMATELY CONSTANT EXTERNAL DIASTOLIC VOLUME

EXPERIMENT	DIASTOLIC VOL. CHANGE DUE TO Ca (C.C.)	OXYGEN CONS. (CAL./MIN.)		PER CENT INC. IN O ₂ CONS. CORRECTED	EFFICIENCY PER CENT		PER CENT INC. EFFICIENCY CORRECTED
		CONTROL	AFTER Ca		CONTROL	AFTER Ca	
4/ 6/34	-0.2	32.9	45.3	47	4.52	7.97	65
4/13/34	-1.1	45.4	55.6	28	2.80	5.42	85

control the diastolic ventricular volume. In the frog's heart Gottschalk³⁷ found that g-strophanthin (ouabain) decreased the oxygen consumption and the work output at a constant, high filling pressure. In the same preparation Eismayer and Quineke³⁵ observed an increased oxygen consumption with doses of strophanthin (Kombé) that produced no change in work output and, with larger doses, decreased oxygen consumption, work output, and efficiency. In the mammalian heart Rohde and Ogawa³³ found that, at approximately constant diastolic volume, strophanthin increased the oxygen consumption proportionately to the change in the isometric pulse pressure-pulse rate product without change in the utilization of the total energy liberated. The marked change in oxygen consumption may be related to the use of Ringer-Locke solution as the

perfusion fluid. In the experiments of Rühl and Wiehler³⁸ in which, unfortunately, the diastolic volume was uncontrolled, the oxygen consumption increased in the majority of experiments, and, on the average, there was no change in efficiency. Gremels,²¹ using the method of Starling and Vischer, but without controlling ventricular volume, found a decreased oxygen consumption and an increased efficiency in hearts treated with strophanthin and lanadigin.

It is obvious that definite and significant results could be obtained only if the diastolic ventricular volume were maintained constant. The effects of glucosides of the digitalis series on the oxygen consumption and external efficiency of the heart under these conditions are summarized in Table VI. The changes recorded represent the maximum effect of the drug before irregularities occurred. They are probably an index of the maximum therapeutic action under the conditions used.

TABLE VI

EFFECT OF GLUCOSIDES OF THE DIGITALIS SERIES ON ENERGY EXCHANGES IN THE HEART AT CONSTANT EXTERNAL DIASTOLIC VOLUME

EXPERIMENT	DRUG USED	OXYGEN CONS. (CAL./MIN.)		INC. IN O ₂ CONS. PER CENT	VOLUME OUTPUT (C.C./MIN.)		EFFICIENCY PER CENT		INC. IN EFFICIENCY PER CENT
		CON-TROL	AFTER DRUG		CON-TROL	AFTER DRUG	CON-TROL	AFTER DRUG	
6/16/33	Scillaren 0.0002 gm.	23.2	41.0	77	333	1200	4.61	14.00	204*
6/ 3/33	Scillaren-B 0.000125 gm.	35.2	50.0	42	739	1428	7.56	16.00	112†
2/ 9/35	Scillaren-B 0.00025 gm.	31.9	48.4	52	242	715	2.23	5.35	140‡
3/15/35	Scillaren-B 0.0002 gm.	42.7	49.6	16	286	666	1.84	4.65	153‡
3/23/35	Ouabain 0.000125 gm.	32.6	48.1	48	500	969	5.58	8.90	60‡
4/ 6/35	Ouabain 0.0001 gm.	26.2	30.8	18	400	750	4.45	8.46	90‡
5/24/35	Digilanid 0.0012 gm.	34.0	39.7	17	625	968	5.88	9.60	63‡

*Following injection of ethyl alcohol.

†Following injection of ethyl alcohol and calcium.

‡In the spontaneously hypodynamic heart.

In all of these experiments both the total energy liberation and the external efficiency are definitely increased. The changes in external efficiency are far too large to be due to changes in the coronary or pulmonary circulations. They reflect an increase in true myocardial efficiency.

The quantitative differences between the changes in oxygen consumption seem to be related to the type of failure preceding administration of the drug. In general, the oxygen consumption is markedly increased in recovery when failure was associated with a decrease in the total energy liberation at a given external diastolic volume. Thus, in experiments following administration of alcohol, which experiments in this

laboratory have shown decreases the oxygen consumption at constant diastolic volume, the oxygen consumption rises 42 per cent or more. In the experiments of Feb. 9, 1935, and of March 23, 1935, failure was accompanied by a considerable decrease in oxidative metabolism. Of the three experiments in which the increase in oxygen consumption was 18 per cent or less, failure was due in the experiment of April 6, 1935, entirely to efficiency loss, and in the other two failure was slight and not followed for a sufficiently long time to permit classification. In three experiments, in which the external diastolic volume was well controlled continuously, the course of failure and recovery is indicated in Figs. 10, 11, and 12. The relative significance of changes in oxygen consumption and external efficiency in recovery from different types of failure is well illustrated.

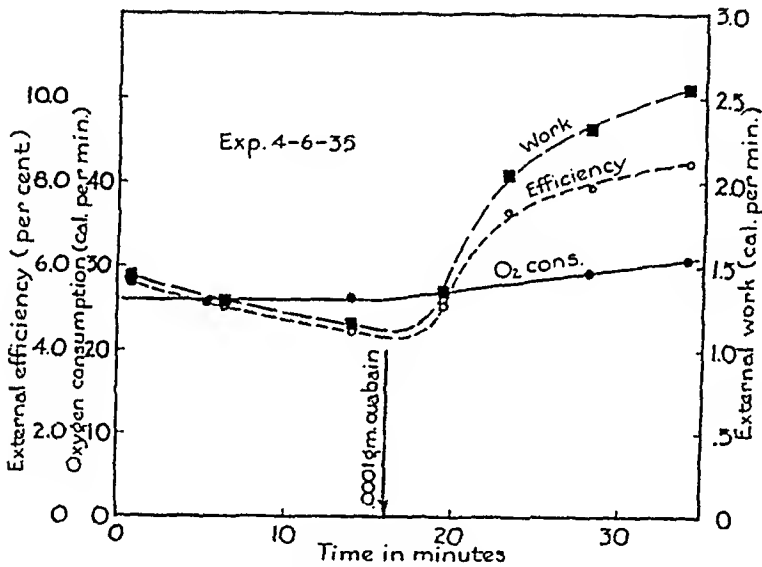


Fig. 10.—Spontaneous failure and recovery due to ouabain at constant external diastolic volume.

It might be expected that recovery from failure due to histamine would exhibit a large increase in oxidative metabolism. This was true in an experiment (Table VII) with strophanthin (Kombé), in which the oxygen consumption increased 60 per cent, although the external diastolic volume decreased. This experiment confirms Rühl and Wiehler.³⁸

TABLE VII

EXPERIMENT OF JUNE 5, 1935

EFFECT OF 0.00025 GM. STROPHANTHIN (KOMBÉ) ON ENERGY EXCHANGES IN THE HEART

OXYGEN CONS. (CAL./MIN.)		INC. IN O ₂ CONS. PER CENT	VOLUME OUTPUT (C.C./MIN.)		EFFICIENCY PER CENT		INC. IN EFFI- CIENCY PER CENT
CONTROL	AFTER S.		CONTROL	AFTER S.	CONTROL	AFTER S.	
18.2	29.3	61	208	500	3.46	5.63	63*

*Following histamine failure.

The change is probably related to a change in heart muscle hydration, as indicated above.

The various cardiac glucosides have actions which differ in the rate at which they take effect and the time of onset of irregularities of rhythm. These properties will undoubtedly influence the relative clinical usefulness of the different agents, and we do not suggest that our findings on the maximum efficiency changes are all that should be taken

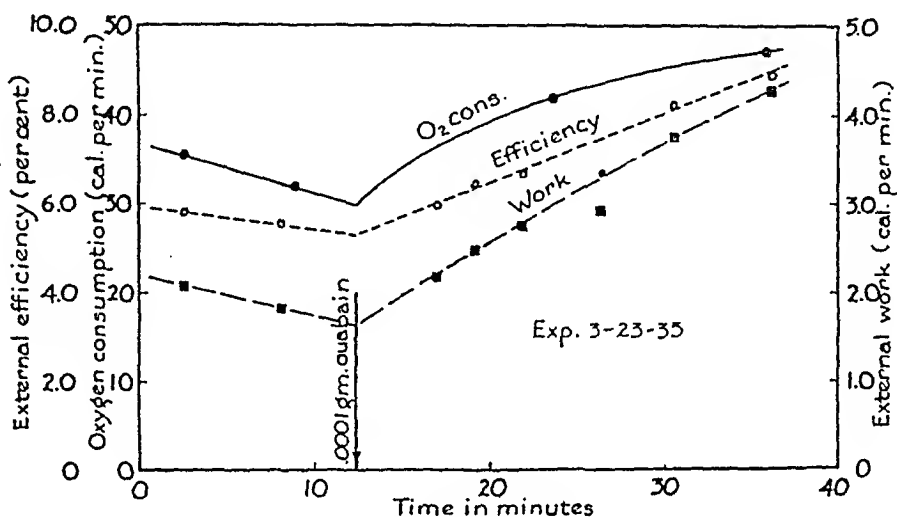


Fig. 11.—Spontaneous failure and recovery due to ouabain at constant external diastolic volume.

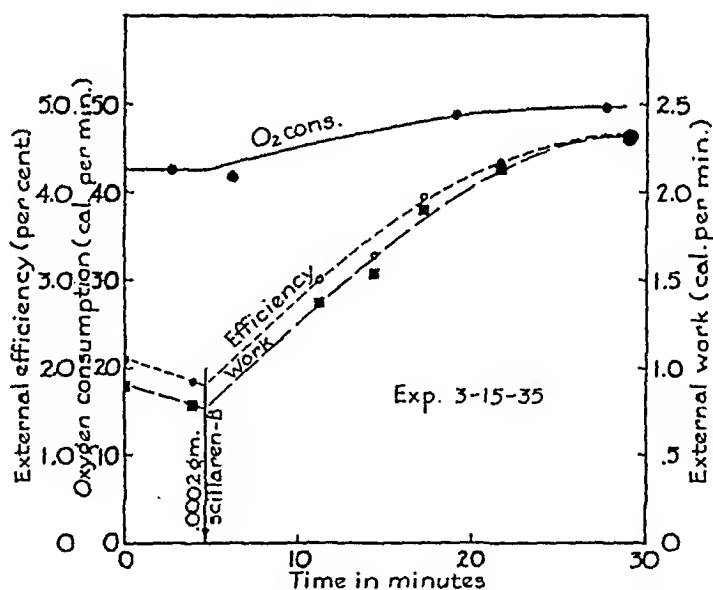


Fig. 12.—Effect of seillaren-B at constant external diastolic volume.

into account in evaluating the usefulness of the several substances. Our main object in this study of the digitalis series of glucosides has been to determine whether they do or do not increase the efficiency with which the heart muscle is able to perform work. In every instance, among the clinically useful glucosides employed, there was an unmistakable increase in efficiency, along with a variable increase in energy liberation. The latter may be due to changes in hydration of the myocardium, but the

changes in mechanical efficiency are independent of that question. These drugs make the heart more economical in its utilization of energy and are therefore conservative in their effect.

The heart-lung preparation is probably not suitable for the final evaluation of the clinical usefulness of every type of cardiac tonic, but it should be very useful in estimating comparative values of agents with essentially similar mechanisms of action. It should also be useful in distinguishing those substances with no beneficial, or actually harmful, actions from those which increase efficiency, the true cardiac tonics. Previous pharmacological assay of such drugs as digitalis has been on the basis of the toxicological action. There is no assurance that the lethal properties are in constant ratio to the useful ones. It would seem to be more reasonable, at least in the trial of new agents, to measure their action upon the essential physiological mechanism for which they are to be employed, namely, in this case, upon the increase in work-capacity of the heart. This emphasis upon the conception of the heart as a working machine with variable efficiency, which should be kept at the highest level practicable, appears to be significant.

SUMMARY

The failing heart has been shown to suffer first simply from a decrease in mechanical efficiency. The energy liberated at a given external diastolic volume remains the same, only the proportion which can be put to useful work falls off. There is in some instances in severe failure a decrease in the oxygen consumption of the heart held at constant external diastolic volume. The hydration of the myocardium under such circumstances has been measured and found to be sufficient to account for the falling off in energy liberation on the basis of the decrease in true mean fiber length when external volume only is kept constant. It is consequently still unnecessary to alter the generalization that initial fiber length governs energy liberation in the failing as well as in the normal heart, when chemical conditions are kept constant.

The importance of the concept of the heart as a machine, doing work, with variable efficiency, has been stressed. Insufficient attention has been given in the past to the concept of efficiency in the physical sense as a criterion of the condition of the heart muscle. These studies appear to prove that myocardial failure consists, in essence, of an alteration of the energy-utilizing and not the energy-liberating mechanism. The machine is able to liberate energy, but it is unable to put it to useful work. The correction of this defect should be the physiological objective in the treatment of myocardial failure.

The effects of several substances upon the heart muscle have been tested from this point of view. Histamine in effective doses decreases the oxygen consumption of the heart-lung preparation in spite of dilatation. This effect is associated with and presumably due to hydration.

Cardiac failure following administration of sodium amytal is due entirely to a decrease in efficiency at constant external diastolic volume. Parathyroid extract increases the oxygen consumption and decreases the external efficiency of the heart. Several reputed cardiac tonics have little or no direct beneficial action on the heart. Coramine produces, instead, dilatation with decreased output and efficiency. Calcium increases the oxygen consumption and efficiency of the heart muscle at constant external diastolic volume. Glucosides of the digitalis series have the same action as calcium, but the maximum effect is delayed.

It has been pointed out that these studies on the digitalis glucosides are significant chiefly in elucidating the mechanism of their action, but that a physiological rather than a toxicological assay of such substances has certain virtues. The methods employed in this study might properly be used in the study of the beneficial action of new agents on the failing heart.

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A RADIOLOGICAL STUDY OF THE PULMONARY ARTERY, WITH SPECIAL REFERENCE TO THE MAIN BRANCHES*

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RADIOLOGICAL visualization of the pulmonary arteries has not received the attention it merits. At present, most conclusions concerning the status of the pulmonary vessels are inferential. In this communication we shall emphasize the feasibility of demonstrating the pulmonary artery itself by means of roentgenology. By this procedure, information concerning the lesser circulation not available through the usual clinical means is obtainable by a direct method.

LITERATURE

During the past fifteen years the literature on the radiography of the heart has contained surprisingly little on the visualization of the pulmonary artery. Frequent mention has been made regarding its appearance in the posteroanterior view,¹⁻⁴ but its demonstration in the oblique positions has received only brief consideration. Inasmuch as the second left arc of the cardiac shadow in the posteroanterior position is formed by both the pulmonary artery and conus, and it is frequently impossible to differentiate between the two, a method whereby the size of the pulmonary artery could be definitely determined should be of the greatest importance.

The English and American literature contains only a few brief descriptions of the appearance of the pulmonary artery in the left oblique projection. Nemet⁴ mentions it briefly in his discussions of the clinical aspects of cardiac fluoroscopy. O'Kane, Andrew, and Warren⁵ show illustrations of the pulmonary artery in post-mortem preparations in the various positions including the left oblique but offer no comment as to its radiographic appearance. A method of approximating the size of the pulmonary artery by its impression against the barium-filled esophagus as seen in the right oblique position is proposed by Parkinson and Bedford.⁶ Their conclusions have been invalidated to a great extent by Hall⁷ for anatomical reasons. We have confirmed at the necropsy table Hall's observation that the pulmonary artery and esophagus are appreciably separated by the bronchus, lymph nodes, and areolar tissue. This precludes intimate approximation of the two structures. Nevertheless, during life an increase in the intensity of the pulsations of the pulmonary artery may cause pressure against these structures and thus on the barium-filled esophagus as seen in the right oblique projection.

The enlarged pulmonary conus is more prominent with rotation into the right oblique view, but the pulmonary artery itself is obscured since

*From the Radiologic Service of Dr. A. J. Bendick and the Medical Service of Dr. L. Lichtwitz, Montefiore Hospital.

it merges into the conus shadow and is no longer border-forming. Enlargement of the right ventricle causes the conus to approach the anterior thoracic wall, finally rotating the entire heart from the right below to the left above. When this rotation is marked, the pulmonary artery is hidden behind the conus even in the posteroanterior view.

The German and French literature contain more adequate discussions on this subject. Assman⁸ describes the vessel in both obliques, and states that it may be completely demonstrated in the left oblique view. Vaquez and Bordet⁹ show illustrations of the pulmonary artery in both oblique positions, including examples of some pathological conditions, such as dilatation and aneurysms. They state that radiography of the pulmonary artery is of definite diagnostic aid in congenital heart disease and in diseases characterized by restriction of the pulmonary circulation. Dietlen¹⁰ favors the posteroanterior view, inasmuch as he was unable at that time to obtain clear radiographs in the oblique positions.

ANATOMY

The pulmonary artery arises from the upper ventral aspect of the portion of the right ventricle known as the conus. It consists of a main trunk and its two primary divisions, the right and left pulmonary arteries, which further subdivide to form the arterial portion of the hila of the lungs. The main stem extends obliquely upward and backward, in a half spiral, first in front, then around, beneath and to the left of the aorta. At the level of the sixth dorsal vertebra it courses posteriorly for 3 or 4 cm., arches over the left main bronchus, and divides into the right and left main branches.

The left pulmonary artery, which is a continuation of the main trunk, is directed posteriorly and to the left. After arching over the left main bronchus, it enters the root of the left lung and subdivides into two branches, which enter their respective lobes almost perpendicularly to the main branch. The right pulmonary artery is the larger and longer of the two. It passes in a horizontal plane behind the aorta and superior vena cava, in front of the esophagus obliquely above the right main bronchus to enter the hilum of the right lung.¹¹

RADIOLOGICAL SIGNS

We have found fluoroscopy to be a satisfactory method of procedure. This may be supplemented by films to confirm the radioscopic findings or for purposes of record. Visualization in the posteroanterior and left oblique views yields the maximum information. The relationships are best demonstrated in individuals with vertical hearts or emphysema, in whom, as a rule, the pulmonary artery is quite prominent. Pressure from above, as from a substernal thyroid, or from below, as from an elevated diaphragm, often accentuates the findings.¹² Various physical factors will increase the visibility of the vessel. Thus, increase in its lumen with resultant increase in the blood volume will cause a denser

shadow to be projected. Sclerosis of the pulmonary vessels secondary to advanced age or prolonged hypertension of the lesser circulation also increases the radiographic density of the vessel. Areas of calcification in the pulmonary artery occasionally may be demonstrated (Fig. 7). The visibility of the artery may be indirectly increased by diminished density of the surrounding lung fields, as is often seen in emphysema or asthma.

The pulmonary artery forms the upper border of the second or middle curve of the left cardiac silhouette in the posteroanterior view. The lower portion of this curve is formed by the pulmonary conus. Only occasionally is it possible to differentiate clearly the two structures. The mesial surface of the pulmonary artery lies against the aorta and heart, and the border of the artery is lost in the denser cardiac shadows.

The hilum as seen in the posteroanterior view is chiefly arterial in structure and consists mainly of the bifurcation of the right and left pulmonary arteries into upper and lower branches and its subdivisions. This fact has been established by Assman,¹³ who ligated the pulmonary artery in dogs and caused a rapid, complete disappearance of the hilar shadows. Weingartner¹⁴ confirmed this by placing thin chains within the trachea and main bronchi and demonstrating that the bronchial shadows were distinctly mesial to the hilar shadows.

Close inspection of the hilum during fluoroscopic examination will reveal clearly expansile pulsations in many normal subjects. This is graphically increased in instances of marked difference between the systolic and diastolic pulmonary pressures, such as is encountered in pulmonic insufficiency when the "hilar dance" is most active.¹⁵ This phenomenon cannot be considered an evidence of pulmonary arteriosclerosis.¹⁶ Increased pulse pressure in the major circulation as seen in instances of aortic insufficiency or hypertension may likewise be reflected in the lesser circulation as exaggerated hilar impulses.

Certain anatomical factors explain the predominance of the arterial components in the production of the hilar shadows. On subdividing, the proximal branches of the pulmonary arteries are directed anteriorly and posteriorly, and since they are projected perpendicularly on the screen, they cause denser shadows than the pulmonary veins which run parallel to the screen and mesial in the posteroanterior view. In addition, the thicker walls and larger caliber of the arterial vessels render them more opaque than the thinner walled veins.

The right hilum is readily discernible in the posteroanterior view as a comma-shaped shadow lying immediately lateral to the midportion of the right heart border. Its width in normal individuals varies between 9 and 15 mm.¹⁷ Its exact localization is facilitated by tracing the air column of the right main bronchus. This band of decreased density separates the cardiac shadow from the hilum. Visualization of the left hilum is often obscured by the overlying pulmonary conus and artery. It may be more easily distinguished in the vertical or hypoplastic type of

heart. Secondary and tertiary branches of the pulmonary vessels leave the hila as arborizations. These represent venous as well as arterial ramifications.

In the left oblique position it is possible to demonstrate the main trunk and left pulmonary artery as a shadow band of lesser density than the aorta obliquely traversing the space immediately beneath and to the left of the aorta, coming to lie just above the left main bronchus. Rotation into this oblique position throws the pulmonic artery clear of the heart shadow. Frequently the first portion of the right main trunk may also



Fig. 1.—H. S., a fifty-eight-year-old man with generalized arteriosclerosis and syphilis. No signs or symptoms of cardiac failure. The roentgenogram shows the normal pulmonary artery well demonstrated in the left oblique view. Fluoroscopic observation shows the pulsations of the vessel.

be demonstrated. The larger portion of the right trunk, however, is lost against the denser shadows of the mediastinum (Figs. 1 and 2).

The bifurcation of the trunk and the right branch of the pulmonary artery is visualized orthoradiographically in the right oblique position. It is seen on end as the "pulmonal fleck," an oval pulsating shadow lying mesial to the aorta and just above the right main bronchus.

PATHOLOGICAL PULMONARY ARTERY

Variations in the size of the pulmonary arteries may be either congenital or acquired. Congenital defects may cause either hypoplasia or

dilatation. Acquired changes are usually dilatation secondary to a lesion within the heart or beyond the main trunks. Hypoplasia as a result of acquired infection is rare. The dynamic effects dilating the pulmonary artery and conus during life may not be demonstrable at the necropsy table (Fig. 3).

Dilatation of the proximal portion of the pulmonary artery may follow hypertrophy of the right ventricle, as frequently occurs when dilatation of the aorta follows left ventricular hypertrophy. Any condition which increases the work of the right heart may eventually lead to dilatation of



Fig. 2.—Pulmonary artery outlined with barium paste. The specimen is turned into the left oblique view.

the main trunks of the pulmonary artery. Protracted right ventricular strain resulting from disturbances of the intracardiac dynamics (left ventricular failure or mitral stenosis) or from increased resistance in the pulmonary circulation (pulmonary arterial disease) illustrates the above point.

Dilatation of the proximal branches of the pulmonary artery is frequently present in pathological conditions, notably myoeardial failure. Temporary dilatation of the hilar vessels followed by return to normal size has been described in failure of the left ventricle associated with paroxysmal tachycardia and in diphtheritic myoearditis with heart fail-

ure.⁸ Assman believes that during left ventricular failure the hilar shadows exhibit a more demonstrable dilatation than the pulmonic trunks and that compensation is marked by a striking diminution in the size of the hilum. We have often observed that patients in chronic cardiac insufficiency show permanently dilated hilar vessels. Improvement in these patients is characterized by a clearing of the previously mottled lung fields rather than by any demonstrable changes in the appearance of the hilar branches.

Clinical and experimental findings support the observation that obstruction as proximal as the divisions of the main trunks¹⁸ or as distal as the pulmonic veins¹⁹ may lead to dilatation of the pulmonary arteries. Peripheral obstruction in the pulmonary circulation is most frequently



Fig. 3.—M. K., an eighteen-year-old schoolboy with rheumatic cardiovalvular disease of ten years' duration. The roentgenogram shows dilatation of the second arch of the left cardiac border (pulmonary artery and conus). Fluoroscopy confirmed the finding of dilatation of the pulmonary artery, especially the main trunk and left main branch. At autopsy the degree of dilatation of the vessel was less than was demonstrated radiologically. These findings indicate that dynamic dilatation seen during life may be absent at autopsy.

responsible for dilatation of the pulmonary artery and its proximal branches. Obstruction to the free passage of blood through the mitral valve results in elevated pulmonary arterial tension, with increased strain on the right heart. Following conus enlargement, the vessel responds to the increased strain by dilatation which may assume huge proportions. (Figs. 4 and 5.)

Pathological conditions in the lung, such as emphysematous, endarteri-
tie, atherosclerotic, or fibrotic lesions, produce increased pressure in the
lesser circulation with similar dilatation of the pulmonary artery. Mac-



A.



B.

Fig. 4.—A. S., a forty-six-year-old housewife with rheumatic cardiovalvular disease of forty years' duration. Admitted in congestive failure. A, x-ray in the postero-anterior view shows dilatation of the second left arch. B, the dilated pulmonary artery is seen in the left oblique view, passing beneath the aorta. The size of the aorta may be estimated by its impression against the barium-filled esophagus. The pulmonary artery is about twice the size of the aorta at its origin. Fluoroscopy confirmed these findings.

Callum²⁰ reported a case of widespread obliterative endarteritis in a thirty-year-old negress who was shown to have a dilated and thickened pulmonary artery at necropsy. Waring and Yegge²¹ published a case of emphysema with pulmonary fibrosis which at necropsy likewise was shown to have a markedly dilated pulmonary artery. Sokoloff and Stewart²² reported a case of hyperplastic sclerosis of the pulmonary artery and arterioles producing a terminal picture of the "black cardiac" type. At necropsy a tremendous hypertrophy of the right ventricle with dilatation of the first part of the pulmonary artery was found. In none of these cases were the radiological findings of the pulmonary artery described in detail.

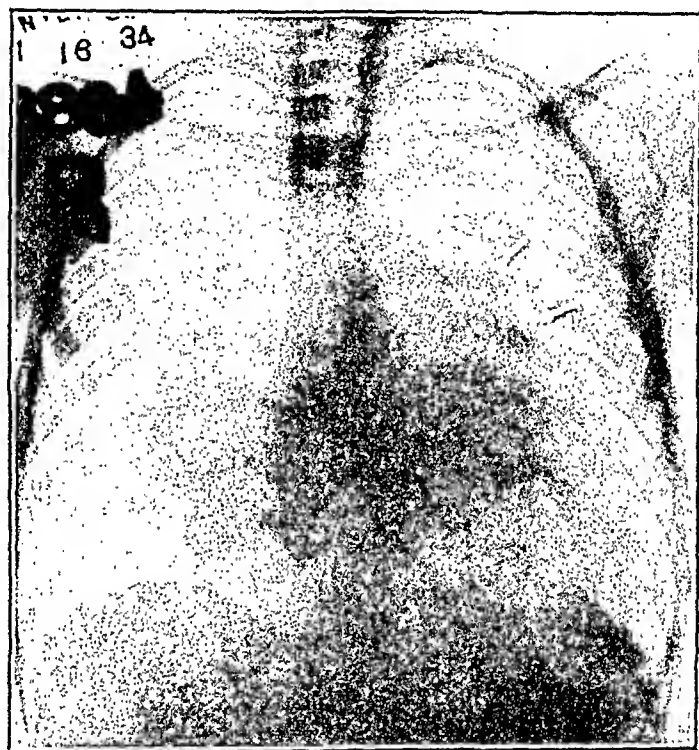
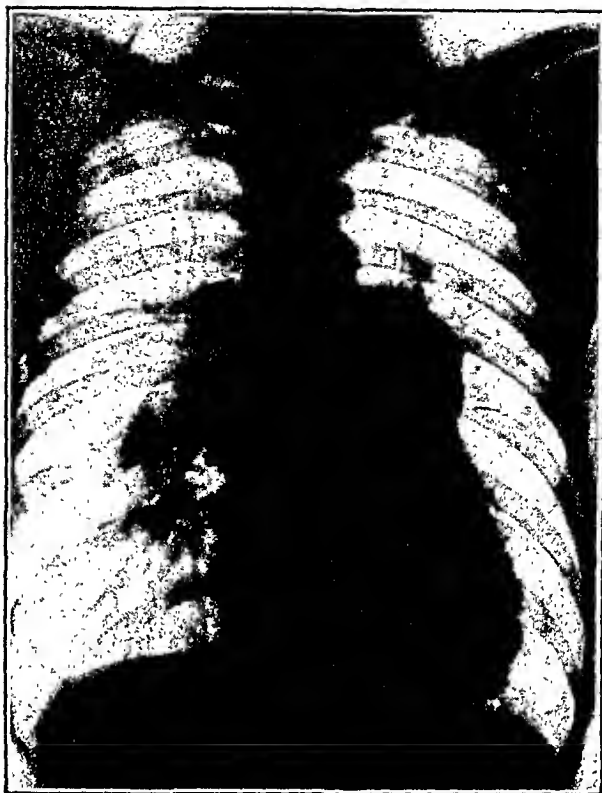


Fig. 5.—J. T., a seven-year-old schoolboy with rheumatic cardiovalvular disease for two years. Patient in persistent cardiac failure. The roentgenogram shows generalized cardiac enlargement and excessive dilatation of the left main branch of the pulmonary artery. The aorta is not seen in this view, indicating rotation of the heart. These findings were confirmed fluoroscopically and at autopsy.

True aneurysmal dilatation of the pulmonary artery is a rare condition²³ and is even more rarely diagnosed during life. It is usually present on a congenital or syphilitic basis²⁴ and involves the main trunk in 85 per cent of the cases reported. Syphilis may even cause a combination of dilatation and narrowing of the main trunks, as in a case described by Karsner.²⁵

Congenital defects of the heart may produce either broadening or narrowing of the pulmonary artery. In Abbott's²⁶ series of 859 proved cases, 297, or 35 per cent, showed abnormalities of the vessel. Dilatation was the more frequent defect, occurring 182 times. It is most marked in cases with interauricular septal defects.²⁷ Frequently the same general



A.



B.

Fig. 6.—H. S., a fifty-seven-year-old man with no history indicative of cardiac disease. A, x-ray in the posteroanterior view shows dilatation of the second left arch. B, in the right oblique view the right main branch of the pulmonary artery is seen passing beneath the aorta. These films were taken during a routine examination.

type of lesion may produce either dilatation or hypoplasia as, for instance, in pulmonary stenosis. Out of 96 cases in Abbott's series, 57 showed hypoplasia, and 17 dilatation. In other conditions, such as patent ductus arteriosus, there were 39 instances of dilatation and none of hypoplasia. It can readily be seen of what diagnostic import definite information concerning the size and position of the great vessels may be.

A prominent pulmonary artery segment in the posteroanterior view is frequently seen in young adults with vertical hearts and in normal children with the globular type of heart. This deviation from the usual picture has no clinical significance.²⁸ A more marked dilatation of the pulmonary artery and its lesser branches is often found with no other

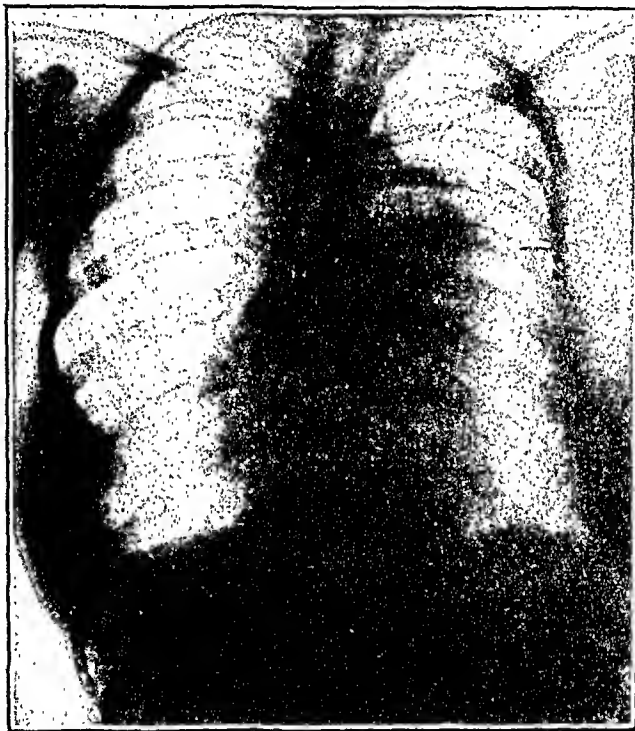


Fig. 7.—I. S., a twenty-three-year-old girl with a lifelong history of marked cyanosis of the lips and fingers and greatly diminished exercise tolerance. X-ray plate in the posteroanterior view shows the left main branch of the pulmonary artery to be markedly enlarged in its proximal portion, with visible areas of calcification. The right ventricle is markedly enlarged. Fluoroscopy confirms these findings. Diagnosis: congenital heart disease.

clinical findings. This may be evidence for congenital heart disease to fit in with the rest of the clinical picture (Figs. 6 and 7).

SUMMARY

It is our object to emphasize the fact that it is possible to visualize roentgenologically not only the pulmonary artery, but also its main branches in most normal and in many abnormal cases. The shadow of the main trunk and left pulmonary artery can usually be seen in properly exposed films taken in the left oblique position, or fluoroscopically. Obstruction anywhere in the pulmonary circulation (whether functional, as in congestive failure, or organic) will lead to dilatation of the pulmo-

nary artery and its major and lesser branches. The size of the pulmonary artery and its lesser branches is of value in recognizing congenital lesions of the heart or pulmonary arterial system in the absence of clinical signs. Radioscopic examination can supply information not obtainable by other clinical means.

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OBSERVATIONS ON THE MECHANISM OF THE DYING HEART IN PATIENTS WITH THE ADAMS-STOKES SYNDROME DUE TO STANDSTILL OF THE VENTRICLES*

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TWO patients with episodes of syncope due to standstill of the ventricles were studied during numerous attacks. In both patients we obtained graphic records of the cardiac mechanism for several hours before death. The clinical manifestations associated with the changes in the rhythm of the heart are so unusual that they deserve attention.

CASE 1.—A. S., a sixty-eight-year-old male, was in good health until May, 1934, when he suddenly lost consciousness for a few minutes. Three months later frequent

episodes of unconsciousness recurred, and he was admitted with signs of congestive heart failure to the Mount Sinai Hospital, where his condition improved. He remained free from these seizures until November, 1932, when he entered the Montefiore Hospital.

On admission he showed slight cyanosis of the lips, marked distention of the neck veins, and prominent carotid artery pulsations. The chest was of the emphysematous type, and the lungs were hyperresonant throughout. The heart was slightly enlarged to the left. The rhythm was regular with a rate of 30 beats per minute. The first heart sound was weak and distant and was obscured by a soft, blowing systolic murmur. The second aortic sound was definitely accentuated. The blood pressure measured 210/80. The liver edge was felt 6 cm. below the costal margin. There was no edema of the lower extremities.

X-ray and fluoroscopic examination of the heart showed a markedly enlarged left ventricle with moderate enlargement of the inflow tract of the right ventricle. The aorta was elongated and tortuous. The electrocardiogram showed complete auriculoventricular dissociation, with a ventricular rate of 30 beats per minute. The form and shape of the QRS complexes varied from beat to beat.

From July, 1934, the patient required occasional doses of salyrgan to control his increasing congestive failure. He was comfortable until October 17, when he developed signs of consolidation at the left base of the lung with a rise of temperature of 105° F. Dullness, bronchial breathing, and bronchophony then appeared over the left upper lobe. His condition grew rapidly worse for one week, and he developed recurring periods of standstill of the ventricles, alternating with periods of ventricular tachycardia. Although he received small doses of epinephrine hydrochloride (1:1600) during several periods of ventricular standstill, he died with the ventricles in standstill.

During the periods of ventricular standstill, the patient became hyperpneic, and the respiratory rate increased rapidly to 40 per minute. After a half minute to a minute following the return of ventricular activity, the hyperpnea gradually subsided and apnea set in. The periods of hyperpnea with ventricular standstill were followed by periods of apnea and tachycardia. Continuous electrocardiograms were taken for long periods during the last three hours of life.

The periods of ventricular acceleration (ventricular rate to 120 beats per minute) were at times suddenly replaced by periods of ventricular standstill. At other

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times there was a gradual slowing of the ventricular rate, and the rhythm was interrupted by ectopic ventricular beats. Standstill of the ventricles then followed for periods varying from one-half to three minutes. During such episodes, the patient became increasingly cyanotic, and then convulsive seizures appeared. These disappeared with the return of the heartbeat.

The electrocardiograms (Fig. 1) obtained at this time revealed ventricular standstill alternating with ventricular tachycardia. The periods of ventricular standstill from which the patient recovered lasted from one-half to three minutes. The standstill period was frequently terminated by an aberrant beat which, in turn, was followed by another short period of standstill (Fig. 1, *B*). This second period of ventricular standstill was followed by a group of aberrant ventricular beats and was ushered in by a period of ventricular tachycardia, with a rate varying from 60 to 120 beats per minute (Fig. 1, *C*). At other times, the post-standstill period of the ventricles was followed by a regular slow ventricular rhythm with a rate of 40 to 60 beats per minute, which was later interrupted by widely aberrant ventricular beats.

About two and one-half hours after the onset of these recurring Adams-Stokes seizures, the electrocardiograms showed a regular rhythmic movement of the string (Fig. 1, *D*). These impulses are probably auricular in origin. This activity continued until four aberrant ventricular beats, each different in form and shape and measuring from 0.2 to 0.4 second (Fig. 1, *E*), interrupted this rhythm. During all this time, no heart sounds were audible, and no pulse could be palpated. The electrocardiogram then resumed the previous activity for a short period, the rate being as high as 150 beats per minute (Fig. 1, *F*). This activity then slowly subsided, became less regular and less frequent, and finally the string stopped (Fig. 1, *G*). This entire episode, from the time the last heart sound was heard until the string stopped moving, lasted twenty minutes.

CASE 2.—S. A., a thirty-nine-year-old male, was in good health until November, 1932, when he had an attack of influenza. At this time a slow heart rate was first noticed, and he complained of dizziness and faintness. For a short period there was a spontaneous return to normal heart rate. Eighteen months later he again developed a slow heart rate with dizziness and faintness. At this time he had several convulsive seizures which were accompanied by a loss of consciousness. Thyroid extract and ephedrine were given daily without relief. He was admitted to the Mount Sinai Hospital on April 13, 1934.

On admission the patient appeared to be well nourished. The left pupil was larger than the right, and there was a marked venous pulsation in the neck with a rate of 65 to 70 per minute. The heart was not enlarged to percussion; the heart sounds were of good quality. There was a long, rough, systolic murmur heard all over the precordium. The heart rhythm was regular and the rate ranged from 20 to 25 beats per minute. The blood pressure registered 175/85. After exercise the auricular rate increased from 70 to 90 beats per minute, and the ventricular rate from 25 to 30-35 beats per minute. The electrocardiograms obtained at this time showed complete auriculoventricular dissociation.

Following the administration of 7 minims of epinephrine hydrochloride (1:1000) at a time when the ventricular rate was 25 beats per minute, the increase in the rate was only 7 beats per minute. The venous pressure was 7.75 cm.; the speed of circulation from the arm veins to the tongue as measured by the saccharine method was 40 seconds, and the speed of the circulation from the arm veins to the lungs as measured by the ether method was 22 seconds. The vital capacity was 3800 c.c. The blood Wassermann reaction was negative.

The patient was comfortable until the fourth day after admission to the hospital, when he suffered a period of dizziness followed by loss of consciousness which lasted seventeen seconds. Epinephrine hydrochloride (1:1000) was given subcutaneously

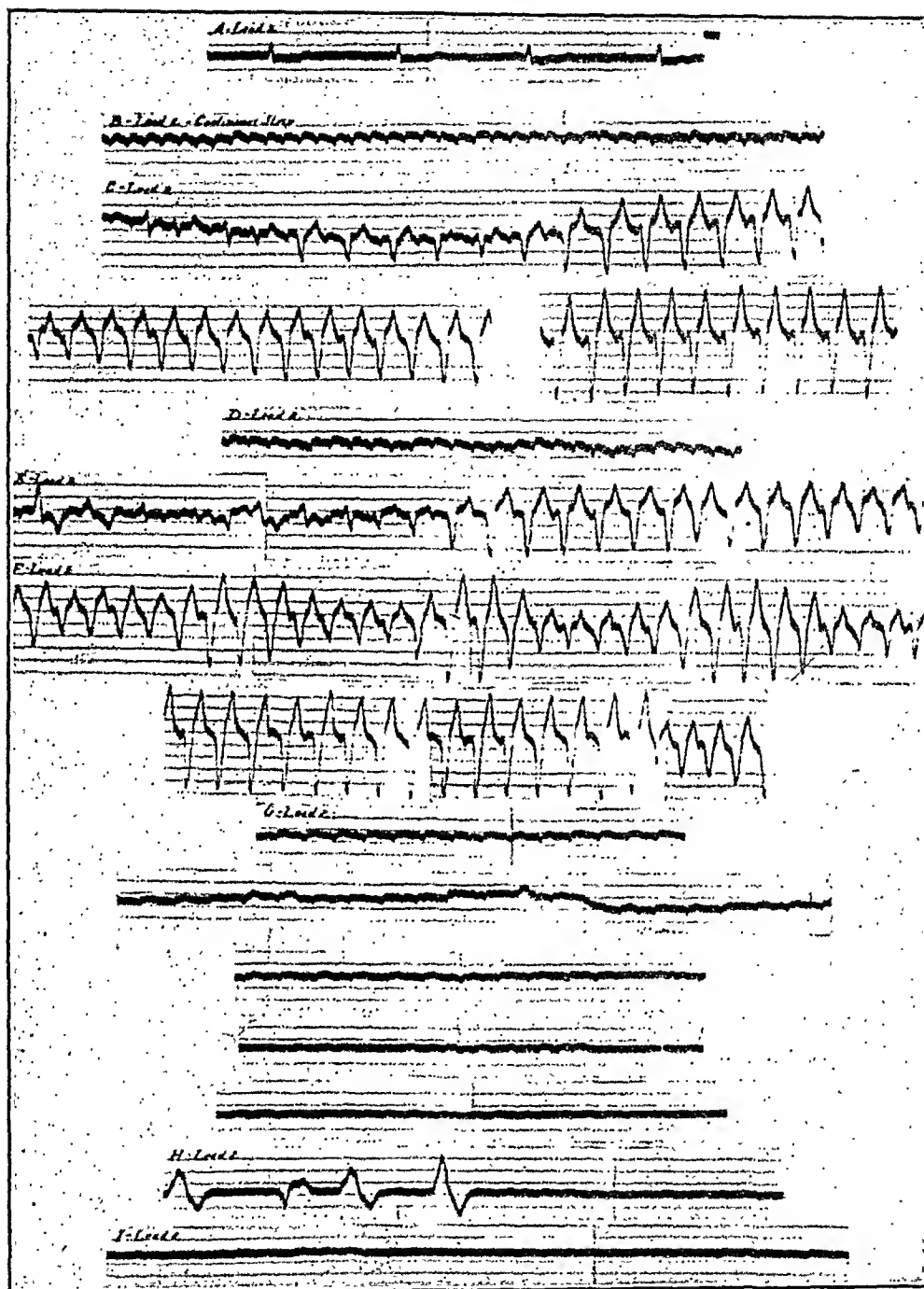


Fig. 1.—A, basic rhythm. Complete auriculoventricular dissociation. Auricular rate 63 beats per minute. Ventricular rate 28 beats per minute.

B, ventricular standstill. Auricular rate 165 beats per minute.

C, transition from ventricular standstill to ventricular tachycardia. Ventricular rate varies from 60 to 120 beats per minute. Auricular rate 150 beats per minute.

D, ventricular standstill. Auricular rate 160 beats per minute.

E, transition from ventricular standstill to ventricular tachycardia, showing multiple ectopic ventricular beats ending the ventricular standstill and initiating the ventricular tachycardia. Auricular rate 150 beats per minute. Ventricular rate 60 to 120 beats per minute.

F, ventricular tachycardia. Ventricular rate 135 beats per minute.

G, recurring ventricular standstill. Note the auricular waves gradually lose their form and shape. The auricular rate slows from 150 to 100 beats per minute.

H, four aberrant ventricular complexes temporarily interrupt the terminal period of ventricular standstill.

I, continuous.

at a time when the heart sounds could not be heard. The ventricular rate speedily increased to a maximum of 120 beats per minute. The rhythm was regular. The ventricular rate then gradually slowed, and numerous premature beats interrupted the rhythm. When the ventricles had slowed to 20 beats per minute, the patient again became dizzy, and, as the rate continued to fall, he lost consciousness. He recovered from this episode and remained well until two days later when he again lost consciousness. This time short periods of unconsciousness recurred at frequent intervals. Each attack lasted from one-half to three minutes. The intervals between attacks were sometimes as short as one-half to one minute. Cheyne-Stokes respiration was noted at this time. During the period of unconsciousness, dyspnea and hyperpnea were present; during the periods of consciousness, apnea was present. There were no heart sounds audible during the periods of unconsciousness. A regular ventricular rate, ranging between 60 and 120 beats per minute, was present during the periods of consciousness. At times a transient period of irregular heart rhythm was noted before and after the attack of unconsciousness.

Electrocardiograms taken during the periods of syncope showed only auricular complexes. The periods of ventricular standstill which were recorded ranged from one-half to one minute. The periods of standstill were abruptly ended by an ectopic ventricular complex, and this was followed by short periods of ventricular standstill which were in turn followed by normal ventricular complexes.

At first the rhythm was irregular, the irregularity being produced by occasional premature beats interrupting the normal ventricular rhythm. The ventricular rate then gradually increased, and frequent aberrant ventricular complexes interrupted the basic ventricular rhythm. When the ventricular rate reached 40 or 50 beats per minute, an ectopic focus in the ventricle superseded the idioventricular pacemaker and the ventricular rate increased to 75 to 120 beats per minute. This ventricular tachycardia gradually slowed, and normal complexes, interrupted by abnormal ventricular complexes, were again seen. The ventricular rate fell to 20 to 25 beats per minute when another period of ventricular standstill followed. Such periods of ventricular acceleration and standstill continued until the patient's death. About 20 minutes before the cessation of electrocardiographic activity, heart sounds could no longer be heard and respirations ceased. After about five minutes, when no ventricular complexes could be seen on the electrocardiogram, three isolated aberrant ventricular complexes, each measuring from 0.2 to 0.4 second were noted, but no persistent ventricular activity followed. The string again became motionless and remained so.

DISCUSSION

In 1912 Cohn and Lewis¹ described a case of complete heart-block and Adams-Stokes syndrome that showed alternating periods of standstill and of tachycardia of the ventricles. Unfortunately, no electrocardiograms were reported by them. Bäumlér² and Hill and MacKinnon³ have described cases of Cheyne-Stokes respiration associated with the Adams-Stokes seizures. Steele and Anthony,⁴ in a recent review of the relationship between Cheyne-Stokes respirations and changes in the cardiac rhythm, described a case of heart-block occurring during the period of hyperpnea. They attributed to variations in vagal activity the association of hyperpnea with standstill of the heart or slowing of the heart, and apnea with tachycardia. This explanation may be correct in cases in which the dominant rhythm is of sinus origin, but in cases of complete heart-block this is questionable.

The problem of vagal influence in complete heart-block was studied

experimentally by Erlanger and Hirschfelder⁵ and again by Cushny.⁶ These observers concluded that in complete heart-block the effects of vagal action on the ventricles could not be demonstrated. They found that the state of nutrition of the idioventricular pacemaker and the influence of ectopic foci in the ventricles on the pacemaker were responsible for changes in the ventricular rate. They also concluded that an ectopic focus in the ventricles (stimulated electrically) beating at a rapid rate depresses the idioventricular pacemaker so that, at the end of a paroxysm of tachycardia, there is a period of ventricular standstill. When the idioventricular pacemaker is continually fatigued by frequently recurring episodes of ectopic ventricular tachycardia, long periods of ventricular standstill are noted when the tachycardia ceases.

The application of these findings to our cases and to the case of Cohn and Lewis suggests that the ventricular standstill is not caused by vagal action, but by depression of the auriculoventricular node brought on by the ectopic ventricular focus beating at a rapid rate. The effect of this mechanism on respirations can be explained on the following basis.

During the period of ventricular standstill, the CO_2 content of the blood rises, and the O_2 unsaturation increases. As a result, the respirations increase in rate. When the heart again beats and washes the CO_2 from the blood, the diminution in the CO_2 content of the blood is insufficient to stimulate the respiratory center and produces apnea. (The hyperpnea with the ventricles at standstill cannot lower the systemic CO_2 content.) This explanation is also offered by Hill and MacKinnon in their studies of a case of Adams-Stokes syndrome and Cheyne-Stokes respirations where the ventricular rhythm is initiated in both bundle-branches of His.

Both cases reported in this communication were studied several hours before death. Whether a similar mechanism occurs in patients with the Adams-Stokes syndrome who recover for long periods of time is not known. It is interesting, however, to point out that epinephrine will initiate a ventricular tachycardia in cases of heart-block, which may be followed by standstill of the heart following the dissipation of the action of the drug. Thus, it would seem important to administer epinephrine only in small doses in cases of Adams-Stokes disease of this type. The administration of large doses of this drug may initiate a ventricular tachycardia of long duration which would be followed by ventricular standstill. The further administration of epinephrine at such a time will initiate a ventricular tachycardia and may again be followed by a longer period of standstill. In this way, recurring episodes of ventricular standstill can be produced. This mechanism may explain the succession of events in our two cases.

The problem of epinephrine administration in these cases is puzzling. Epinephrine is usually given during the period of ventricular standstill. The drug certainly cannot act directly on the ventricular muscle (unless

injected intracardially) since there is no circulation at this time. The action of epinephrine by stimulation of the sympathetic fibers at the local point of administration of the drug and then by its continued action on the central sympathetic trunk may explain the action of the drug on the ventricles at a time when there is no circulation. The administration of a large dose of epinephrine may at first stimulate the ventricles by this neurogenic mechanism and then, with the return of the ventricular contractions, absorption of the drug into the blood stream may then produce the direct action on the sympathetic endings in the ventricle itself. The sympathetic action on the lower centers below the auriculo-ventricular node may produce a rapid ventricular rate, ectopic in origin, which may displace the idioventricular pacemaker and finally depress it so that standstill will occur at the end of this paroxysm of tachycardia. Thus, the continuous or repeated administration of epinephrine in such cases appears to be contraindicated, even when the episodes of standstill are frequent.

SUMMARY

Two cases of recurring episodes of standstill of the heart alternating with ventricular tachycardia are described. The period of ventricular standstill is associated with dyspnea and hyperpnea; the tachycardia is associated with apnea.

The association of Adams-Stokes disease and Cheyne-Stokes respiration is discussed. It is suggested that changes in vagal action are not the cause of the recurring episodes of standstill of the heart and of ventricular tachycardia.

The mechanism of the action of epinephrine during the period of ventricular standstill is probably a neurogenic mechanism from the point of administration through the central sympathetic trunk to the sympathetic endings in the ventricles.

It is suggested that only small doses of epinephrine be used in cases of standstill of the heart since large doses may induce periods of long ventricular tachycardia and result in recurring episodes of standstill of the heart. The continuous administration of even dilute solutions of epinephrine in such cases seems to be contraindicated.

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BACTERIAL ENDOCARDITIS WITH SPECIAL REFERENCE TO THE CARDIAC IRREGULARITIES

A CLINICAL AND PATHOLOGICAL STUDY OF 191 CASES*

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IT IS generally agreed that rhythmic disturbances are rare in the course of active bacterial endocarditis. Libman¹ in 1918 first commented that "arrhythmia is remarkably infrequent." With the increase in bacterial endocarditis cases there have appeared more specific references to the occurrence of cardiac irregularities in the course of the disease.

AURICULAR FIBRILLATION IN THE COURSE OF SUBACUTE BACTERIAL ENDOCARDITIS

The rarity of auricular fibrillation in the course of subacute bacterial endocarditis was noted in the reports by Cotton,³ Mason,⁴ Blumer,⁵ Thayer,^{6, 7} Bierring,⁸ Horder,^{9, 10} Rothschild, Sacks, and Libman,¹¹ Morrison,¹² Hurxthal,¹³ Fulton and Levine,¹⁶ Davis and Weiss²⁶ and Segal.⁴³ The occurrence of subacute bacterial endocarditis and auricular fibrillation in patients with preexisting auricular fibrillation has been observed by Sprague,¹⁴ Winternitz,¹⁵ Laws and Levine¹⁷ and de la Chapelle and Graef.¹⁸

The extensive studies of Libman, Thayer, Blumer, and Horder and others have fairly well established the dicta:

1. That in subacute bacterial endocarditis the heart maintains its functional capacity in a remarkable manner.
2. That auricular fibrillation rarely supervenes in the course of subacute bacterial endocarditis.
3. That subacute bacterial endocarditis rarely supervenes in a patient with preexisting auricular fibrillation and valvular disease.

AURICULAR FLUTTER IN THE COURSE OF SUBACUTE BACTERIAL ENDOCARDITIS

This irregularity occurs less frequently than auricular fibrillation. Few references were found in the literature. Blumer⁵ mentioned one case in his comprehensive review but gave no details of the case. Rothschild, Sacks and Libman¹¹ mentioned one instance which occurred in a bacteria-free, inactive case.

De la Chapelle and Graef¹⁹ reported a case of active subacute bacterial endocarditis in a thirty-three-year-old male in which auricular flutter was recorded ten weeks before death, but did not reappear. On admission the rhythm was normal except for premature beats. No Aschoff bodies were found in the microscopic sections.

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The author⁴³ reported the occurrence of auricular flutter and fibrillation in a thirty-eight-year-old female with active subacute bacterial endocarditis thirteen days before death. The rhythm was normal on admission. After the recorded flutter the rhythm remained normal except for ventricular extrasystoles and a sino-auricular tachycardia. At autopsy no Aschoff bodies were found in the microscopic sections.

In a study of sixty-five cases of auricular flutter, McMillan and Bellet²⁰ found no cases of subacute bacterial endocarditis. Sixteen of their cases occurred in patients with rheumatic heart disease, an incidence of 24.6 per cent. The remaining cases occurred in syphilitic, hypertensive, toxic myocarditis, thyrotoxic, and drug poisoning cases.

CONDUCTION DISTURBANCES IN SUBACUTE BACTERIAL ENDOCARDITIS

Changes in conduction time in the course of active subacute bacterial endocarditis have been observed infrequently.^{12, 13, 14, 16, 19, 21} Rothschild, Sacks, and Libman¹¹ and Levy and Turner²² made comparative electrocardiographic studies of conduction disturbances in rheumatic fever and subacute bacterial endocarditis.

In their 65 rheumatic fever cases, Rothschild, Sacks, and Libman¹¹ found 23 with prolongation of the P-R interval, an incidence of 35.3 per cent. In their 61 cases of active subacute bacterial endocarditis, they found 10 with prolongation of P-R intervals varying from 0.21 to 0.36 sec., an incidence of 16.4 per cent. Changes in the ventricular complexes were found even less frequently in the subacute bacterial endocarditis cases. In these they found inconspicuous alterations consisting of slight notching and slurring of the QRS complex.

Levy and Turner,²² in their 403 cases of rheumatic fever, found 112 with prolongation of the P-R interval, an incidence of 27.8 per cent. In their 23 subacute bacterial endocarditis cases, they found 3 with prolongation of the P-R interval without block, an incidence of 13 per cent. Two of these cases were permanent during observations. Digitalis and salicylate effects were considered ruled out. Swift²³ found an increased P-R interval in 70 out of 81 cases of rheumatic fever. He used a less rigid criterion for prolongation and dealt with much sicker patients.

Winternitz¹⁵ made frequent electrocardiographic studies in sixty-nine cases of mycotic endocarditis. He found only one case with prolongation of the P-R interval. Autopsy revealed extensive ulcerative involvement of the aortic valve, congenital aneurysm of the right auricular septum, and involvement of the tricuspid valve. Sections showed invasion of the bundle of His.

Longcope²⁴ discussed the differentiation of acute rheumatic fever from bacterial endocarditis and stressed the infrequency of alteration of the cardiac mechanism in bacterial endocarditis as compared with its frequency in rheumatic fever. In a series of twenty-one cases of subacute

bacterial endocarditis, two cases (9.5 per cent) of prolonged P-R interval were found. This is a lower incidence than the 16.4 per cent observed by Libman and the 13 per cent noted by Levy and Turner.

RELATIONSHIP OF AURICULAR FIBRILLATION AND SUBACUTE BACTERIAL ENDOCARDITIS

Libman and his school were the first to point out the infrequency of auricular fibrillation in the course of subacute bacterial endocarditis and the rarity of subacute bacterial endocarditis in patients with preexisting auricular fibrillation. Levine²⁵ offered an explanation for the rarity of subacute bacterial endocarditis in rheumatic patients with persistent fibrillation and in patients with congestive heart failure. He pointed out that most of the latter group at autopsy showed dense and fibrous mitral leaflets, whereas in the subacute bacterial endocarditis group the mitral valves more often give the appearance of having been in a fair state of health before the development of the terminal infection. He stated that the dense fibrous leaflets acted as an inhibitory factor to bacterial invasion. In a later paper Fulton and Levine¹⁶ offered an explanation for the fact that patients with high grade mitral stenosis possessed an apparent immunity to bacterial endocarditis. They attributed this to the persistence of a local rheumatic process in the mitral valve which might be antagonistic to the development of bacterial endocarditis.

Davis and Weiss²⁶ made a study of thirty-five cases of subacute bacterial endocarditis which came to autopsy. They found only two cases of auricular fibrillation. They noted that a very mild endocardial lesion was apparently as predisposing to subacute bacterial endocarditis as was an advanced lesion. In the rheumatic hearts which came to autopsy, they found more cases with mild than with advanced lesions. They considered that this statistical finding would explain the comparative infrequency of severe mitral stenosis in subacute bacterial endocarditis. They noted further that this predominance of mild rheumatic heart lesions explained the infrequency of auricular fibrillation in subacute bacterial endocarditis since auricular fibrillation was found to be more commonly associated with advanced rheumatic damage.

Laws and Levine¹⁷ felt that the great disparity and antagonism between these two conditions could not be explained in the above manner. They wrote that there were "a large number of patients with persistent auricular fibrillation and valvular disease who live on the average for several years. If the bacterial invasion of damaged valves were a mere accident, it is surprising that there are not more instances of subacute bacterial endocarditis in patients with fibrillation. The same holds true of congestive failure."

De la Chapelle and Graef, having previously expressed an interest in this relationship, approached the problem by making a study of the vary-

ing grades of mitral stenosis in rheumatic heart disease in relation to the occurrence of auricular fibrillation.

De la Chapelle, Graef, and Rottino²⁷ made a clinical pathological study of 119 rheumatic hearts with special reference to auricular fibrillation. They found that forty-two had auricular fibrillation, an incidence of 35.3 per cent. This is somewhat lower than the 57 per cent incidence noted by Davis and Weiss²⁶ in their series of every variety of rheumatic heart disease, including cases of paroxysmal auricular fibrillation. It is likewise lower than the 53 per cent incidence in the series of 100 cases of severe mitral stenosis reported by Stone and Feil.²⁸

De la Chapelle and his associates concluded that the two types of hearts which appeared to be immune to subacute bacterial endocarditis, those with auricular fibrillation and those with severe mitral stenosis, bore no relation to each other except that some degree of stenosis or insufficiency was necessary for the development of auricular fibrillation. The grade of stenosis was not found to be related to the presence of auricular fibrillation. It would appear difficult to draw such a conclusion inasmuch as 75 per cent of their patients died of congestive heart failure, and the incidence of congestive failure was not listed in the moderately and severely stenotic groups. It is generally believed that auricular fibrillation commonly occurs in failing hearts and those which have had episodes of failure. If there were many such cases in their moderately stenotic group, the incidence of fibrillation would rise appreciably. Their conclusions are contrary to the often expressed opinion that auricular fibrillation is more common in mitral stenosis of the more advanced type. The rarity of severe mitral stenosis in subacute bacterial endocarditis has been used to explain the infrequency of auricular fibrillation in this disease.

From the above, it would appear difficult to correlate auricular fibrillation with the grade of mitral stenosis without considering the integrity of the myocardium as a whole. The pathogenesis of auricular fibrillation is intimately related to the underlying anatomical changes, the changes in circulatory dynamics, and the possibility of altered chemical "environmental changes." Physiological and anatomical investigations have not been conclusive. The studies of Yater²⁹ and of Mohler and Crawford³⁰ failed to reveal any characteristic of auricular fibrillation which might be considered distinctive or of itself responsible for the onset and continuation of auricular fibrillation.

The anatomical changes in the myocardium in subacute bacterial endocarditis have been the subject of much discussion. Blumer and others have stated that the myocardium is rarely involved. Horder and others have called the disease an "endocarditis vera" in contrast to rheumatic heart disease in which the endocardium, myocardium, and pericardium are usually involved. On the other hand, Clawson,^{31, 32} Libman^{33, 34} and Saphir³⁵ have emphasized the frequent occurrence of myocardial lesions

in subacute bacterial endocarditis. The coexistence of recent rheumatic infection (Aschoff bodies) in hearts from patients dying of subacute bacterial endocarditis has been observed by Libman,² Saphir and Wile,³⁶ by Saphir,³⁵ and by von Glahn and Pappenheimer.³⁷ This seems to indicate a more frequent involvement of the integrity of the myocardium in subacute bacterial endocarditis than has been hitherto supposed.

ANALYSIS OF CASES

All the clinical and autopsied cases of bacterial endocarditis from 1906 through 1934 in the Boston City Hospital were reviewed. Only those cases with bacteriological confirmation were included. The material was subdivided into two groups.*

I. Cases of subacute bacterial endocarditis, including only *Streptococcus viridans* and *Bacillus influenzae*.

II. Cases of bacterial endocarditis with a large variety of organisms.

I. Subacute Bacterial Endocarditis

There were 108 cases, of which 92 were fatal. There were 47 autopsies. Of the cases 61 occurred in males and 47 in females. The ages varied from ten to sixty-three years, with an average of thirty-two years. The average female age was thirty. The average male age was thirty-five. Of the cases included, only 6 occurred between 1909 and 1922. The remaining 102 dated from 1923 (when the first electrocardiograms were recorded) through 1934.

Bacteriology.—All cases were in the active (bacterial) stage of the disease. In 91 cases, positive blood cultures for *Streptococcus viridans* were obtained during life. No blood cultures were taken in 9 cases. Blood cultures were negative in 7. In one case *Bacillus influenzae* was obtained.

Autopsy Findings.—The typical vegetations of subacute bacterial endocarditis were found in all cases. In the few patients who did not have positive blood cultures when alive, post-mortem cultures confirmed the diagnosis. In 47 autopsied cases, involvement was for the most part in the following valves.

TABLE I
VALVES INVOLVED

Mitral alone	18	40.0* per cent
Aortic alone	9	20.0* per cent
Mitral and aortic	13	28.8* per cent

*In general, the figures are similar to those of Clawson and Bell,³⁸ Blumer,⁵ Fulton and Levine,¹⁶ Thayer,⁷ and Davis and Weiss³⁹ in this country. They differ, however, from the postbellum cases found on the Continent in which there was a large incidence of aortic involvement, reported by Coombs,⁴⁰ Cotton,³ Starling,⁴¹ Morawitz,⁴² and Horder.⁹

*A portion of this autopsy material had been previously utilized in the study by Davis and Weiss.³⁹

No attempt was made to analyze the various grades of mitral stenosis because of the difficulties in drawing conclusions from valves measured by different observers with varying technique. Previous damage was present in a large percentage of the cases.

Clinical Past Histories.—Forty patients gave histories of rheumatic fever. Fifteen had knowledge of rheumatic heart disease. Twelve gave histories of frequent tonsillitis, 5 of "rheumatism," 2 of chorea and rheumatic fever, 3 of "heart disease," 4 of "chorea," 1 of congenital syphilis, and 1 of scarlet fever. In 10 cases no past history could be obtained, and in 7 there was no history of rheumatic infection.

In 25 cases, the time intervening from the first rheumatic fever attack to the complicating subacute bacterial endocarditis varied from five months to thirty-five years, an average of 10.3 years. This differs from the interval of 17.5 years in the series of Fulton and Levine.¹⁶ In 10 of the patients with cardiac irregularities, an average of well over ten years was obtained for this period. The ages of this group varied from twenty-one through fifty-four years.

Rhythm.—Electrocardiographic studies were obtained in 49 of the cases. In the remaining 59 cases, an evaluation was made of repeated

TABLE II
OBSERVATIONS IN THE CLINICALLY STUDIED CASES

NO. OF CASES	OBSERVATION
50	Regular rhythm at all times
3	Gallop rhythm at times
3	Occasional extrasystoles
1	"Irregular pulse" shortly before death
1	Auricular fibrillation for 3 weeks prior to death

TABLE III
OBSERVATIONS IN THE ELECTROCARDIOGRAPHED CASES

NO. OF CASES	OBSERVATION
3	Sinus arrhythmia
15	Sino-auricular tachycardia
2	T-waves indicative of myocardial disease
11	Left ventricular predominance
2	Right ventricular predominance
1	Occasional ventricular premature beats
4	Partial heart-block and left ventricular predominance
1	Partial heart-block, intraventricular block, and left ventricular predominance
1	Partial heart-block, coronary T-waves
1	Partial heart-block, premature beats
1	Partial heart-block and prolonged Q-T interval
1	Partial heart-block and later auricular fibrillation
1	Complete heart-block and partial heart-block
1	Complete heart-block, left bundle-branch block and occasional premature nodal beats
1	Developed auricular flutter which persisted throughout
1	Normal rhythm, then auricular flutter and fibrillation prior to death
1	Preexisting established auricular fibrillation

clinical observations from past and present records in this and in other hospitals. We believe these observations to be sufficiently valid to be included.

In addition to the cases listed in Tables II and III, clinical observations revealed one case with extrasystoles and gallop rhythm, two cases with occasional extrasystoles, and two cases with gallop rhythm.

TABLE IV
COMBINING BOTH CLINICAL AND ELECTROCARDIOGRAPHIC OBSERVATIONS

NO. OF CASES	OBSERVATION
18	Left ventricular predominance
3	Right ventricular predominance
11	Heart-block
1	Left bundle-branch block
1	Prolonged Q-T interval
8	Occasional premature beats
1	Occasional nodal premature beats
4	"Pathological T-waves"
6	Gallop rhythm
2	Auricular flutter
3	Auricular fibrillation

During the course of the observed irregularities, eight of the heart-block cases received no digitalis prior to the block, and eight cases received only "adequate" amounts. In two of the latter, digitalis was discontinued when the heart-block was recognized. Two cases received small amounts of salicylates, the others none. The flutter and fibrillation cases received digitalis at times.

In the group showing heart-block, the irregularity was observed repeatedly in serial electrocardiograms in a few cases. In the others, two or three electrocardiograms were obtained, but were not always continued to the time of death.

Valves Involved at Autopsy.—Of the cases demonstrating heart-block, fibrillation or flutter, six were autopsied.

TABLE V

TYPE OF CASE	VALVES INVOLVED
Partial heart-block	Mitral and aortic
Partial heart-block	Aortic alone (syphilitic)
Complete heart-block	Aortic and pulmonic
Complete heart-block*	Mitral and aortic
Partial heart-block and auricular fibrillation	Mitral and aortic. (Mitral valve measured 12.1 cm. in circumference and was not stenosed.)
Auricular flutter and fibrillation	Mitral and aortic. (Mitral valve measured 9.5 cm. in circumference and was moderately stenosed.)

*Patient received digitalis (not included).

There were no Aschoff bodies found in the microscopic sections in any of these cases.

TABLE VI

VALVES INVOLVED AS SHOWN BY CLINICAL EVIDENCE IN NONAUTOPSIED CASES

TYPE OF CASE	VALVES INVOLVED
1 Complete heart-block	Mitral and aortic
3 Partial heart-blocks	Mitral and aortic
3 Partial heart-blocks	Aortic
2 Auricular fibrillation	Mitral
1 Auricular flutter	Mitral

Table VII compares the incidence of valve involvement with normal rhythm as compared to those with heart-block.

TABLE VII

AUTOPSY EVIDENCE

VALVES INVOLVED	AUTOPSIED CASES WITH NORMAL RHYTHM		5 AUTOPSIED CASES WITH HEART-BLOCK	
Mitral alone	18	45.0 per cent	0	0
Aortic alone	8	20.0 per cent	2*	40 per cent
Mitral and aortic	10	25.0 per cent	2	33 per cent
Pulmonic and aortic	0	0	1	20 per cent
M., A., and tricuspid	3	7.5 per cent	0	0
Tricuspid	1	2.5 per cent	0	0
Total mitral involvement	31	77.7 per cent	2	40 per cent
Total aortic involvement	21	52.5 per cent	5	100 per cent

*Includes one case of partial heart-block found in the acute bacterial group.

The most striking finding is that of no involvement of the mitral valve alone in the heart-block group as compared to a 45 per cent involvement in the group with normal rhythm. The involvement of the aortic valve alone and in combination was higher than in the group with normal rhythm. The marked predilection for the aortic valve, with disturbances in conduction time, was also found in the previously mentioned cases by De la Chapelle, Libman and his coworkers, and Winternitz.

The involvement of the aortic valve was found most often in those cases with disturbances in conduction time, particularly disturbances of the P-R interval. It was noted less frequently in cases showing no rhythmic abnormalities in the course of subacute bacterial endocarditis. The same applies when comparison is made to the flutter and fibrillation group in which the involvement seemed to occur in the mitral valve alone or in the mitral and aortic valves.

This frequency of aortic involvement in the heart-block group would appear to be in keeping with the observations of Tawara who pointed out the close relationship of the bundle of His to the anterior and right posterior aortic cusps.

It may be assumed that the irregularities were due entirely to the subacute bacterial endocarditis, inasmuch as no Aschoff bodies were found in the microscopic sections.

II. Acute Bacterial Endocarditis

There were 84 patients studied in this group. Eighty-one died, and 3 were discharged, unrelieved, at their own request. Autopsies were performed in 73 cases. There were 56 males and 28 females. The average age was thirty-four years, with a range from seventeen months through seventy-three years. The average age of the males was thirty-eight years. That of the females was twenty-six years.

In a large percentage of this group the acute bacterial endocarditis was not recognized clinically but was demonstrated at autopsy. This is in contrast to the subacute bacterial endocarditis group, in the majority of whom the diagnosis was made clinically. Many in the group ran a clinical course typical of subacute bacterial endocarditis and were excluded from Group I only because bacteriological evidence of *Streptococcus viridans* or influenza bacteria was lacking and because other organisms were found at autopsy. Twenty-five of the cases were found in the years 1906 through 1920. The remaining sixty-one occurred from 1921 through 1934.

Bacteriological Findings.—Blood cultures were taken during life in 34 cases and the organisms found were as follows: 12 *Streptococcus hemolyticus*, 7 pneumococcus, 6 *Staphylococcus aureus*, 2 meningococcus, 2 gonococcus, 1 Haverhill bacillus, 4 miscellaneous organisms.

Autopsy Findings.—All cases showed the typical vegetations of bacterial endocarditis. The cases included were only those that yielded bacteriological confirmation or demonstrations of organisms in sections. All organisms except *Streptococcus viridans* and *Bacillus influenzae* were included in this group. The majority were the organisms found in the living blood cultures. A small group yielded mixed or unidentified organisms in cultures and sections. In 72 autopsied cases, involvement was, for the most part, as given in Table VIII.

TABLE VIII
VALVES INVOLVED

Aortic alone	27	37.5 per cent*
Mitral alone	18	25.0 per cent*
Mitral and aortic	15	20.8 per cent

*The incidence was reversed as compared to the subacute bacterial endocarditis group.

Past Histories.—Thirty-one patients gave histories of rheumatic fever, "heart disease," "rheumatism," sore throats, or chorea. In 11 cases, no past history was obtained. In 19 cases there was no previous history of rheumatic infection.

In 20 cases of previous rheumatic infections, the years since initial infection ranged from one through thirty years, with an average of 11.5 years.

Rhythm.—Clinical observations were analyzed in 65 cases and electrocardiograms studied in 19 other cases. The results are given in Table IX.

TABLE IX

NUMBER	OBSERVATION
77	Normal, save for sinus arrhythmia or tachycardia
3	Irregularity without classification
1	Terminal auricular fibrillation
3	Gallop rhythm
3	Premature beats
1	Partial heart-block
3	Left ventricular predominance
3	Right ventricular predominance

In Table IX the case demonstrating partial heart-block had vegetations covering a congenital bicuspid aortic valve. No other valves were involved. A predominating gram-negative bacillus was cultured. This case was included in the subacute bacterial endocarditis group with heart-block.

The patient with terminal auricular fibrillation had malignant vegetations on the mitral valve and a purulent meningitis. No other valves were involved. The mitral valve measured 10.2 cm. in circumference and was not stenosed.

TABLE X

P-R INTERVALS IN RHEUMATIC FEVER

AUTHOR	CASES	PROLONGED P-R INTERVALS	
Swift ²³	81	70	86.4 per cent
Levy and Turner ²²	403	112	27.8 per cent
Libman et al. ¹¹	65	23	35.3 per cent
Total	549	205	37.2 per cent

TABLE XI

AURICULAR FIBRILLATION IN RHEUMATIC HEART DISEASE

AUTHOR	TYPE OF CASE	NO.	INCIDENCE OF AURICULAR FIBRILLATION	
Laws and Levine ¹⁷	Died of acute rheumatic carditis	34	12	35.3 per cent
	Died of emboli or thrombus	17	16	94.1 per cent
Winternitz ¹⁵	Rheumatic endocarditis with decompensation	120	88	73.4 per cent
	Rheumatic endocarditis with emboli and infarcts	17	5	28.4 per cent
	Recurrent polyarthritis with old endocarditis	31	2	6.5 per cent
Bierring ⁸	Rheumatic endocarditis	24	3	12.5 per cent
De la Chapelle et al. ²⁷	Rheumatic heart disease	119	42	35.3 per cent
Stone and Feil ²⁸	Severe mitral stenosis	100	53	53.0 per cent
Davis and Weiss ³⁹	Rheumatic heart disease	164	74	57.0 per cent
	Rheumatic heart disease with auricular thrombi	25	22	88.0 per cent
	Total	651	317	48.7 per cent

TABLE XII
CARDIAC IRREGULARITIES IN THE COURSE OF BACTERIAL ENDOCARDITIS

AUTHOR	TYPE OF CASE	NO.	AURICULAR FIBRILLA- TION	AURICU- LAR FLUTTER	PRO- LONGED P-R INTERVAL	ALTERED QRS	BUNDLE- BRANCH BLOCK	GALLOP RHYTHM	PRE- MATURE BEATS	LEFT VENTR. PREDOM- INANCE	RIGHT VENTR. PREDOM- INANCE
Libman et al. ¹¹	Sub. bact. end.	109	1		10	4	1		6		
Cotton ³	Sub. bact. end.	55	1								
Mason ⁴	Sub. bact. end.	1	1								
Blumer ⁵	Sub. bact. end.	301	4	1				1			
Thayer ^{6, 7}	Sub. bact. end.	100	5								
Bierings ⁸	Sub. bact. end.	30	0								
Morrison ¹²	Sub. bact. end.	145	1								
	Acute bact. end.	26	0								
Sprague ¹⁴	Sub. bact. end.	20	1		4	2				2	
Fulton and Levine ¹⁶	Sub. bact. end.	111	1		2	2					
Laws and Levine ¹⁷	Sub. bact. end.	43	1								
Levy and Turner ²²	Sub. bact. end.	23			3						
Winternitz ¹⁵	Sub. bact. end.	35	2								
	Acute bact. end.	69	3		1						
De la Chapelle and Graef ^{18, 19}	Sub. bact. end.	3	1	1	2	1	1	1	1		
Stone and Feil ²⁸	Sub. bact. end.	5	0								
Saphir and Wile ³⁶	Sub. bact. end.	10	0								
Davis and Weiss ²⁶	Sub. bact. end.	35	2								
Coombs ¹⁰	Sub. bact. end.	30	0								
Longcope ²⁴	Bact. end.	21	0		2						
Author	Sub. bact. end.	108	3	2	8	2	1	6	12	18	3
	Acute bact. end.	86	2	0	1						
Total	Sub. bact. end.	1,149	24	4							
Total	Acute bact. end.	202	5	0							
Grand total	Bact. end.	1,351	29	4							

No Aschoff bodies were found in the microscopic sections in either case.

Comparison of the Cardiac Irregularities in Rheumatic Infections and Bacterial Endocarditis

It was considered advisable to tabulate the irregularities in the course of rheumatic fever (Table X), rheumatic heart disease (Table XI), and bacterial endocarditis (Table XII) so that comparisons could be made. The cases included were single reports and those specifically stating the number observed and the irregularity noted.

TABLE XIII
WITH REFERENCE TO AURICULAR FIBRILLATION AND FLUTTER

TYPE OF CASE	NO.	AURICULAR FIBRILLATION		AURICULAR FLUTTER	
Rheumatic heart disease	651	317	48.7 per cent		
Subacute bacterial endocarditis	1,149	24	2.07 per cent	4	0.35%
Acute bacterial endocarditis	202	5	2.47 per cent	0	0
Bacterial endocarditis (Total)	1,351	29	2.14 per cent	4	0.22%

No attempt was made at this time to determine what percentage of rheumatic heart disease cases show auricular flutter. In McMillan and Bellet's²⁰ 65 cases of auricular flutter, 16 occurred in patients with rheumatic heart disease. None occurred in patients with subacute bacterial endocarditis. It cannot be denied that the incidence of 0.22 per cent flutter in the bacterial group is strikingly less than the incidence in rheumatic heart disease. The comparative infrequency of auricular fibrillation and flutter in the course of subacute bacterial endocarditis is impressive.

TABLE XIV
DISTURBANCES IN CONDUCTION TIME

TYPE OF CASE	NO.	PROLONGED P-R INTERVAL		PROLONGED QRS COMPLEX	
Rheumatic fever	549	205	37.2 per cent	Not determined	
Subacute bacterial endocarditis	152	25	16.4 per cent	8	5.3 per cent
Acute bacterial endocarditis	41	3	7.3 per cent	0	0
Bacterial endocarditis	193	28	14.5 per cent	8	4.1 per cent

Left bundle-branch block was observed but once in the author's series. It was mentioned as having occurred in one of De la Chapelle and Graef's reported cases and in one of the series of Libman and his associates. In both of these cases, extensive ulcerative involvement of the aortic valve with extension onto the pulmonic valve was found. Two other cases of bundle-branch block in subacute bacterial endocarditis were included in Graybiel and Sprague's²¹ 395 cases of bundle-branch block with varying etiology. That this abnormality is most unusual in the course of subacute bacterial endocarditis cannot be denied.

With Reference to Axis Deviation.—This finding was sought in sixty-eight electrocardiographed cases of subacute bacterial endocarditis. Twenty had left axis deviation, an incidence of 30 per cent. Only three had right axis deviation, an incidence of 4.4 per cent.

With Reference to Premature Beats.—Three hundred thirty-one cases of subacute bacterial endocarditis, combining both electrocardiographic and clinical evidence, were examined with reference to premature beats. Twenty-two were reported, an incidence of 6.6 per cent.

With Reference to Gallop Rhythm.—Four hundred eight cases of subacute bacterial endocarditis revealed only seven with gallop rhythm, an incidence of 1.7 per cent.

COMMENT

A comparative study of the cardiac irregularities in the course of rheumatic fever, rheumatic heart disease, and bacterial endocarditis revealed the remarkable infrequency with which cardiac irregularities occur in bacterial endocarditis.

A distinct preference for the aortic valve alone or in combination was found in the cases of bacterial endocarditis with heart-block, in contrast to the preference for the mitral valve alone or in combination in the cases with normal rhythm and in those with fibrillation and flutter. The only case of pulmonic involvement occurred in the prolonged P-R interval group and was associated with aortic involvement. The two cases of tricuspid involvement were associated with normal rhythm.

At autopsy the case of left bundle-branch block revealed extensive vegetations on the aortic valves with extension onto the pulmonic cusps. Two other cases were reported by De la Chapelle and Graef¹⁰ and by Libman and his associates.¹¹ These two showed extensive ulcerations involving the aortic cusps with extension to the bundle of His in the latter case.

The case of auricular flutter which later changed to a fibrillation and finally to showers of extrasystoles at autopsy revealed vegetations on the mitral valve with some extension to the aortic valve. The mitral valve was but moderately stenotic and measured 9.5 cm. in circumference. In the case of auricular flutter reported by De la Chapelle and Graef, the mitral valve was moderately thickened, and the orifice was not stenosed.

In a previous study⁴³ the autopsy findings of the present series of cases with auricular fibrillation were compared with other reported cases. When mitral involvement occurred in the course of subacute bacterial endocarditis with flutter or fibrillation, it was usually in the form of moderate stenosis, or else mitral regurgitation. No cases of severe mitral stenosis were found. The circumference of the mitral valves ranged from 9.5 through 12.1 cm. This was also observed in the cases reported in the literature.

It does not seem that the rarity of auricular fibrillation in subacute bacterial endocarditis can be explained entirely by the infrequent occurrence of severe mitral stenosis in this disease or by the usual association of auricular fibrillation with severe mitral stenosis. Over 50 per cent of the patients died of terminal circulatory failure in the present series and in the reported cases of auricular fibrillation or flutter in subacute bacterial endocarditis. It is generally considered that circulatory failure is a rather infrequent complication in the course of subacute bacterial endocarditis.

These observations favor the concept that the occurrence of auricular fibrillation in subacute bacterial endocarditis is directly related to the integrity of the myocardium and to the physiological and biochemical changes underlying the auricular fibrillation rather than to any grade of underlying mitral stenosis per se.

SUMMARY

1. The literature is reviewed with reference to the cardiac irregularities in the course of bacterial endocarditis, rheumatic heart disease, and rheumatic fever.

2. A study of 192 cases of bacterial endocarditis, with electrocardiographic studies in 67 cases, revealed 4 cases of auricular fibrillation, 2 of auricular flutter, 9 of heart-block, 2 of prolonged QRS interval, 1 of prolonged Q-T interval, 1 of left bundle-branch block, 9 of gallop rhythm, 15 of extrasystoles, 21 of left axis deviation and 6 of right axis deviation.

3. Prolongation of the P-R interval occurs more commonly in the cases of bacterial endocarditis with involvement of the aortic valves alone, or in combination, than in cases of mitral involvement.

4. Disturbances in conduction time, particularly intraventricular block and bundle-branch block, are far less common in bacterial endocarditis than in rheumatic heart disease. The same is true of gallop rhythm and premature beats.

5. A statistical study, including all other reported cases, leads one to conclude that auricular fibrillation and auricular flutter are rare in the course of bacterial endocarditis.

6. The occurrence of auricular fibrillation and flutter in the course of bacterial endocarditis appears to be related to the functional integrity of the myocardium rather than to any grade of mitral stenosis in itself.

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THE FOUR-LEAD ELECTROCARDIOGRAM IN TWO HUNDRED NORMAL MEN AND WOMEN* †

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ONE who examines a great number of electrocardiograms learns by experience to distinguish normal variations from those produced by disease. Before a statistical analysis of an abnormal group of records is of any value, however, it is first necessary to determine the averages and ranges of a group of normal records so that they may be used as a basis for comparison. In view of the fact that the various published series of normal records are made up almost exclusively of males,¹⁻⁴ the present series has included an equal number of males and females so that statistical methods might be applied to detect any possible sex variations in voltages, intervals, and wave contours. In addition to the three conventional leads, a chest lead has been used.

The series was composed of two hundred individuals, ranging in age from twenty to thirty-five years; that is, adults below the period of significant arteriosclerotic disease. Averages and ranges of the two sex groups were compiled separately and compared, but the two are reported here as a whole in instances where there is no significant sex difference. The male group was made up entirely of medical students and internes, and the female group was composed chiefly of nurses, with a few technicians, and secretaries. No one was included in the series who gave any history of previous cardiac disease, rheumatic fever, or poor tolerance for exercise. All were examined for abnormal physical signs. Heart size was determined by palpation and percussion and was checked by x-ray examination in instances which will be noted. The blood pressure of all subjects was below 135 systolic and 90 diastolic. A moderately loud systolic murmur was present over the pulmonic area in about 6 per cent, but no individual in whom any other frank murmur could be heard was included. No records were withdrawn from the series because of their not conforming to a conception of the normal electrocardiogram derived from previously published accounts.

Records were made with a "Hindle All Electric" portable electrocardiograph. The subjects were seated with back inclined to 20 degrees from the vertical. The precordial lead was taken from the apex with the "indifferent electrode" applied to the left leg (referred to as Lead IV in this paper). The apex was located as accurately as possible by palpation and percussion. Two additional anterior leads were used in twenty-one subjects in order to determine the effect of electrode position

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on the contour of the complexes. An anteroposterior lead was also employed in thirty cases in order to compare the tracings with those made by the routine leg-apex lead.

Resistance was reduced to 2,000 ohms or below by careful skin preparation to prevent distortion of the waves by overshooting and to keep string tension great enough to maintain a deflection time of 0.02 second or less. Time lines and millimeter lines were recorded on the paper and, with the aid of a magnifying glass, measurements were made with an accuracy of 0.1 mm. The authors believe that for the determination of average values in a given lead an accuracy beyond 0.01 second or 0.1 mm. can rarely be obtained by any method of measurement, as the variations due to inherent differences in complexes and the distortions from string drift and somatic tremor are generally far beyond these limits. All standardizations were 1 cm. = 1 mv.

THE P-WAVE

Measurements of height and duration of the P-wave were taken from that one of the three standard leads in which these values were greatest (Table I). In 90 per cent of the cases, Lead II showed the P-wave of greatest amplitude; the remaining 10 per cent exhibited it about equally in Leads I and III. In the present series the P-wave varied from 0.5 mm. to 2.5 mm. in height. There were six records in which it was above 2.0 mm. and fifteen records in which it was below 1.0 mm. The limits given by Pardee⁴ are 1.0 mm. to 2.0 mm. The average measurement for men in this series was 1.41 mm. and that for women 1.30 mm. If a sex difference actually exists, it is difficult to demonstrate it in a wave of such small amplitude as this. The limits of duration of the P-wave were 0.08 second to 0.12 second for men and women alike with an average of 0.09 second. The largest figure, 0.12 second, occurred in three cases, and in thirteen records the measurement was 0.11 second. There was no demonstrable correlation between the duration of the P-wave and heart rate.

TABLE I
AVERAGES AND LIMITS OBTAINED FROM LEADS I, II, AND III

	HEIGHT OF P (MM.)	DURATION OF P (SEC.)	P-R INTERVAL (SEC.)	HEIGHT OF QRS (MM.)	DURATION OF QRS (SEC.)	HEIGHT OF T (MM.)
Males						
Maximum	2.2	0.12	0.19	19.2	0.12	6.8
Minimum	0.5	0.08	0.12	5.8	0.06	1.4
Average	1.41	0.095	0.14	12.4	0.087	3.3
Females						
Maximum	2.5	0.12	0.18	19.7	0.11	4.5
Minimum	0.7	0.08	0.12	3.6	0.06	0.8
Average	1.30	0.094	0.15	10.8	0.085	2.6
Entire Series						
Maximum	2.5	0.12	0.19	19.7	0.12	6.8
Minimum	0.5	0.08	0.12	3.6	0.06	0.8
Average	1.35	0.095	0.145	11.6	0.086	3.0

In two-thirds of the records the P-wave was smooth and rounded in all leads, but in the remaining third the summit was sharply peaked in one or more leads, usually in Leads I and II. This variation in contour was not related to amplitude. Notching along the course of the P-wave occurred in about 30 per cent of the records and was seen in Lead II or Lead III about twice as frequently as in Lead I. There was also a tendency for the former two leads to be affected together, although only one record was seen in which there was notching in all three leads. No instance was encountered in which the P-wave was notched and exceeded 2.0 mm. in height and 0.10 second in duration, a picture which is characteristically found in mitral stenosis.

Inversion of the P-wave occurred in 5 per cent of the records and was seen only in Lead III. A diphasic P-wave appeared once in Lead II and thirty-one times in Lead III. A correlation has been observed between the incidence of inverted P-waves and of inverted T-waves in Lead III. Thus, of the records showing inverted P_3 , 75 per cent also showed an inverted T_3 , while T_3 was inverted in only 35 per cent of the records of the series as a whole. Furthermore, of the total number of cases with inverted T_3 , 11 per cent showed also an inverted P_3 , whereas for the series as a whole P_3 was inverted in only 5 per cent of the records. The same tendency was found in records with diphasic T- and P-waves in Lead III. A similar correlation was demonstrated between inverted or diphasic P_3 -waves and left axis deviation. There were three records with inversion of P, QRS, and T in Lead III.

In their series of normal records made with a chest lead, Katz and Kissin⁵ and Master⁶ used the anteroposterior position of the electrodes. Master stated that when the posterior electrode position was exchanged for a lead from the left leg in thirty individuals, no significant changes in the electrocardiogram were noticed. This observation has been partially verified on thirty individuals in the present series, but it is of interest that with regard to the P-wave this finding has not been confirmed. When an A-P lead* was used, 90 per cent of the P-waves were inverted, and the remaining were diphasic or isoelectric; while, when the left leg and apex were used, P was upright in 25 per cent of the records, diphasic in 29 per cent, inverted in only 45 per cent, and isoelectric in 1 per cent. In addition to the greater tendency toward inversion, the P-waves by the former method were of greater amplitude and duration (Table II). This should lead one to conclude that the A-P position is apparently more favorable for recording auricular activity. About 8 per cent of the P-waves in records made by the routine leg-apex lead were definitely notched and approximately the same number were affected when the A-P method was used.

*The posterior electrode was applied 4 cm. inside the tip of the left scapula, while the left arm was hanging at the side. The anterior electrode was at the apex. (Anterior electrode right arm terminal, posterior electrode left leg terminal.)

TABLE II
AVERAGES AND LIMITS OBTAINED FROM LEAD IV

	AMPLITUDE OF P (MM.)		DURATION OF P (SEC.)		DURATION OF P-R INTERVAL (SEC.)		HEIGHT OF QRS (Q + R) (MM.)		DURATION OF QRS (SEC.)		AMPLITUDE OF T (MM.)	
	LEG-APEX LEAD	A-P* LEAD	LEG-APEX LEAD	A-P* LEAD	LEG-APEX LEAD	A-P* LEAD	LEG-APEX LEAD	A-P* LEAD	LEG-APEX LEAD	A-P* LEAD	LEG-APEX LEAD	A-P* LEAD
Males												
Maximum	1.0	1.0	0.10	0.12	0.16	---	51.3	41.0	0.11	---	13.0	14.0
Minimum	0	0.2	0.04	0.06	0.10	---	7.4	13.0	0.06	---	1.3	2.0
Average	0.50	0.68	0.07	0.086	0.13	---	19.5	23.6	0.088	---	5.4	6.9
Females												
Maximum	1.4	---	0.09	---	0.16	---	29.5	---	0.11	---	9.2	---
Minimum	0.1	---	0.04	---	0.08	---	4.6	---	0.06	---	0.5	---
Average	0.40	---	0.07	---	0.13	---	12.9	---	0.085	---	3.5	---
Entire Series												
Maximum	1.4	---	0.10	---	0.16	---	51.3	---	0.11	---	13.0	---
Minimum	0	---	0.04	---	0.08	---	4.0	---	0.06	---	0.5	---
Average	0.45	---	0.07	---	0.13	---	16.2	---	0.086	---	4.5	---

*Thirty cases.

THE P-R INTERVAL

In 75 per cent of the records the maximum P-R interval was found in Lead II. The average was 0.15 second, with a minimum of 0.12 second and a maximum of 0.19 second. The latter figure was encountered in only one record. In 90 per cent of the records the measurement was within the range of 0.13 to 0.17 second. Although it is stated that the P-R interval decreases with increasing heart rates,⁴ no significant statistical correlation to this effect could be demonstrated in this series. This does not prove, however, that there may not be such a relation in any one given individual.

A depression of the P-R level below the isoelectric line (sometimes called the auricular T-wave) was present in one or more leads in 95 per cent of the records. The maximum depression, 0.8 mm., was found in Lead II in which the negative deflection appeared in 90 per cent of the records. It occurred in Lead I in 55 per cent of the cases and in Lead III in only 30 per cent. It was combined most frequently in Leads I and II, in 50 per cent of the records, but was seen in both Leads II and III in 17 per cent of the cases and in all three leads in 11 per cent. No instance was encountered in which it was found in Leads I and III together. There were two records in which the P-R level was elevated above the base line to a height of 0.3 mm. in one case (Lead II), and 0.4 mm. in the other (Lead I).

The P-R interval in the leg-apex chest lead tended to be shorter than the maximum found in the conventional leads, averaging 0.13 second with limits of 0.10 second and 0.16 second. Master⁶ found that the auricular T-wave was especially frequent and prominent in the A-P chest lead but in this series, with the leg-apex lead used, a slight deflec-

tion was detectable in only 2 per cent. There was, however, an appreciable elevation in two-thirds of the records taken by the A-P lead, which reached a height of 0.5 mm. in some cases.

THE QRS COMPLEX

The voltage of QRS as determined by the maximum deflection in the standard three leads showed wider limits of variation than are ordinarily recognized (Table I). It is to be noted that the height of QRS of three men and twelve women fell below 7 mm. and that of twelve men and four women exceeded 17 mm. Of the fifteen below 7 mm., about half were in records showing two leads of about equal height with the other lead nearly isoelectric, a type of record in which the lowest possible re-

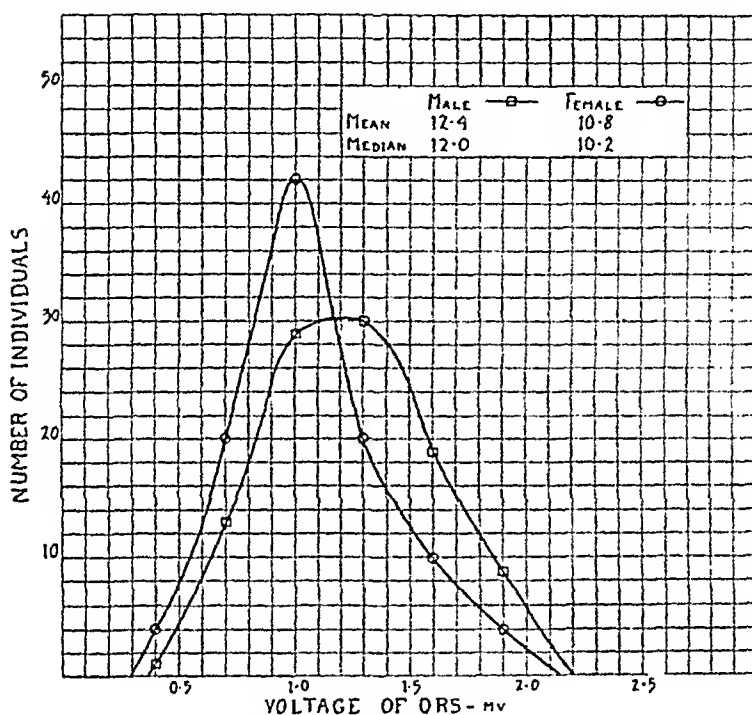


Fig. 1.—Frequency curves showing a sex difference in voltage of QRS (Leads I, II and III). Standard deviation from the mean, males 3.30; females 3.34. (Expressed in tenths of a millivolt as are the mean and median above.) St. D. = $\sqrt{\frac{\sum d^2}{N}}$

cording of the actual manifest potential has been made. There were three in the female group with measurements of 5 mm. or below. The lowest, 3.6 mm., occurred in an individual with slight scoliosis. Fluoroscopic examination, however, revealed nothing but displacement of the heart. Basal metabolism readings were -13 per cent, -14 per cent and -15 per cent. The other two individuals with measurements of 4.8 mm. and 5.0 mm., respectively, also had normal hearts by fluoroscopic examination and had basal metabolic rates of -8 per cent and -12 per cent in the first case, and -15 per cent, -18 per cent and -20 per cent in the other. None of these three individuals had any clinical evidence of hypothyroidism. The voltage of QRS in Lead IV ($Q + R$) measured

9 mm. in the case with the lowest measurement in the conventional leads and 8 mm. and 18 mm., respectively, in the latter two instances. The low voltage in Leads I, II, and III was therefore not found to be associated with a correspondingly low voltage in Lead IV.

A significant sex variation in voltage is illustrated in Fig. 1. Males tend to show a higher voltage than females. The same is true of QRS in Lead IV, which suggests that the sex difference is not due to the effect of a variation in the position of the heart (Table II). The activity of the individuals in both groups was probably about the same. There was no correlation between voltage and body size.

The average duration of QRS was 0.087 second for males and 0.085 second for females, a difference less than that found by McGinn and White.⁷ The maximum figure, 0.12 second, occurred once and 0.11 second twice. The time interval of QRS in Lead IV compared closely with that in the limb leads (Tables I and II).

The presence of a "deep" Q-wave in Lead III in normal subjects has been discussed by several authors.⁸⁻¹² In the present series an initial downward deflection has been called a Q-wave. When records were selected according to the criteria of Pardee,⁸ there were four with a deep Q₃, and these were in the male group. In one case there was left axis deviation, in another a border of left axis deviation, in a third a border of right axis deviation (see discussion under axis deviation), and in the final case no axis deviation was present. T₃ was inverted in three records and diphasic in the fourth. Roentgenograms revealed hearts of normal size and shape, with an anatomical axis within the average range in two cases and a slightly horizontal axis in the other two. In all cases the chest was relatively broad, and the individual was inclined to be stout, but the diaphragm was not considered elevated by the roentgenologist.

No records were encountered with "M" or "W" complexes in Lead II resembling those described by Edeiken and Wolferth.¹³

The conformation of QRS in Lead IV was usually of the Q-R diphasic type, but there were the following exceptions: In eight instances there was only a simple monophasic downward excursion and in four others there was an initial R-wave as high as 3 mm. followed by a deep S-wave. An "M" complex with small initial and terminal positive deflections and a deep negative middle stroke was encountered seventeen times. Thus, in 15 per cent of cases the QRS configuration was not of the usual diphasic type and, although there never occurred a complex with an absent Q-wave and a high initial deflection (above 3 mm.), as is encountered in myocardial infarction, the statement cannot be made that the initial deflection of QRS normally is invariably downward in the leg-apex lead. In the thirty cases in which the A-P lead was used, the QRS complex was always of the simple Q-R type.

The average depth of the Q-wave was 9.7 mm. for the entire series, with a maximum of 33.0 mm. and a minimum of 1.4 mm. The R-wave averaged 7.6 mm. and varied between 31.6 mm. and 0 mm.* Inasmuch as the depth of Q tends to vary inversely with the height of R as the anterior electrode is shifted to either side of the apical position, the sum of Q plus R was determined in order to lessen the effect of errors associated with the localization of the apex (Table II).

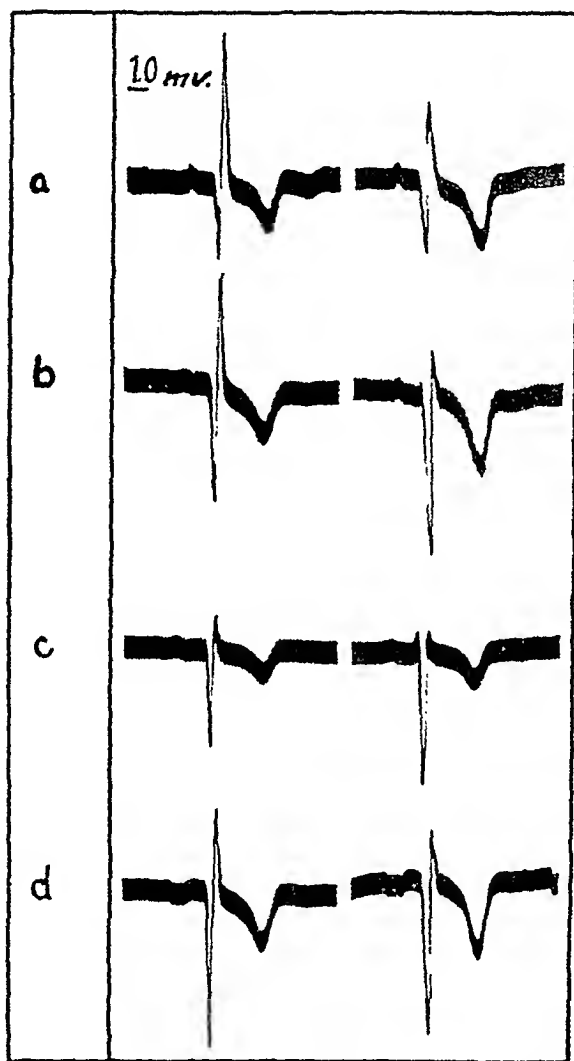


Fig. 2.—Chest lead tracings from two individuals. The “indifferent electrode” was placed on the left leg for complexes *a*, *b* and *c*. Curve *a* was made with the anterior electrode at the fourth interspace 1 cm. to the left of the sternal margin, *b* was obtained with the electrode at the apex in the fifth interspace, and *c* with the electrode in the sixth interspace at the anterior axillary line. The A-P lead with the anterior electrode at the apex was used for the tracing *d*.

In twenty-one subjects characteristic changes occurred¹⁴ when the “indifferent electrode” was applied to the left leg and the “exploring electrode” was placed successively over points at the fourth interspace 1 cm. from the left margin of the sternum, at the apex in the fifth interspace, and at the sixth interspace along the anterior axillary line (Table

*Complexes with a small initial upstroke (including “M” complexes) were excluded from these tabulations.

TABLE III
COMPARISON OF THE FOUR METHODS OF LEADING FROM THE CHEST TO SHOW THE EFFECT ON THE QRS AND T DEFLECTIONS
(MEASUREMENTS IN MILLIMETERS)

	FOURTH INTERSPACE AND LEFT LEG						APEX AND LEFT LEG						SIXTH INTERSPACE AND LEFT LEG						ANTEROPOSTERIOR					
	Q			R			Q+R			T			Q			R			Q+R			T		
	Q	R	T	Q	R	T	Q	R	T	Q	R	T	Q	R	T	Q	R	T	Q	R	T	Q	R	T
Average	6.5	32.0	4.9	11.1	9.4	19.5	5.7	8.5	5.9	14.3	2.9	13.0	10.0	23.6	6.9	1.0	1.5	13.0	2.0	1.0	1.5	13.0	2.0	2.0
Maximum	13.0	35.0	9.0	23.0	25.0	38.0	11.0	15.0	8.0	23.0	5.0	28.0	24.0	41.0	14.0	1.0	1.5	13.0	2.0	1.0	1.5	13.0	2.0	2.0
Minimum	2.5	9.0	15.0	5.0	1.0	8.0	1.0	3.0	3.0	10.0	0	3.0	3.0	10.0	0	1.0	1.5	13.0	2.0	1.0	1.5	13.0	2.0	2.0
Number of "M," "W," "R-S," type or Vibratory	1 "W"						5 "M"						14 "M," "R-S," and Vibratory						0					

III). The excursions were larger when the fourth interspace position was used and became progressively smaller as the electrode was moved out and down to the other two positions. Near the sternal margin at the fourth interspace R was relatively high, measuring two to three times the depth of Q, at the apex Q and R were about equal, while at the anterior axillary line Q was invariably larger than R. The parasternal position yielded one "W" complex (5 per cent) with Q- and S-waves approaching one-third the height of R. The apex position gave five (25 per cent) "M" complexes as described above, while the extreme lateral position produced eight "M" complexes and three other complexes in which a small initial R-wave was followed by a deep S-wave (50 per cent) (Fig. 2). It is evident that alterations from the simple Q-R form are much more frequent in lateral than in medial positions.

SLURRING AND NOTCHING OF QRS

Slurring is caused by a momentary retardation of string movement and is visible as an isolated point of thickening along the course of the complex. Notching is produced by an actual change in direction of

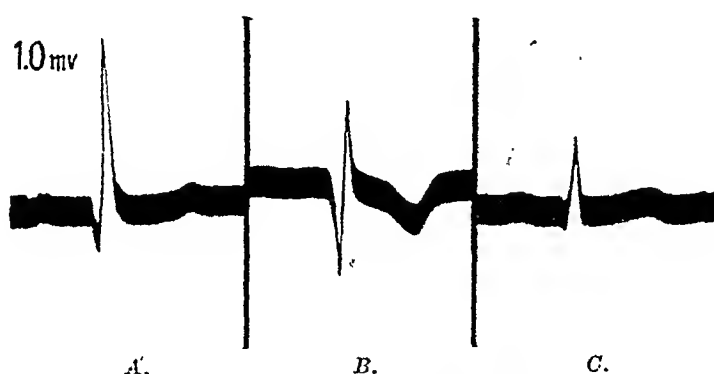


Fig. 3.—Illustration of three common types of thickening of QRS which are often confused with slurring.

string movement. Both of these deformities are caused by the same phenomenon, namely, some alteration in the magnitude or change in direction of the progression of electrical potential within the myocardium.

Before the incidence and nature of slurring and notching are discussed, another type of thickening of the limbs of QRS should be noted because it is often confused with true slurring and leads to erroneous interpretations of records. This type of thickening is not due to any electrical disturbance within the myocardium. It is present when string motion is uniformly slow and is characterized by a smooth, even widening of a limb of a complex, which is the result of the recording system used in the usual string galvanometer. Three common manifestations of this thickening are illustrated in Fig. 3. The first type is seen in complexes where the string gradually accelerates or retards as it leaves or returns to the base line (Fig. 3, A). The second is present as a

thickening of the initial and final strokes of a diphasic complex (Fig. 3, *B*). The third is seen in the complex of low amplitude where there has been no associated narrowing of the QRS interval (Fig. 3, *C*). (A prolonged QRS interval produces the same effect in complexes of average height.)

In the present series the location of the point of slurring or notching and the height of the involved complexes have been noted, for these deformities are generally considered to be of more diagnostic significance when seen remote from the base line in complexes of relatively high amplitude. There have been included as slurring only those instances where the point of thickening was present in each successive complex and definite enough not to be doubted by any observer. Irregularities resulting from artefacts or from a superimposed somatic tremor were avoided.

Thirteen cases showed slurring or notching in Lead I. In five instances this consisted of very slight thickening at the peak of an R-wave, 7 to 11 mm. in height. In seven other instances there was definite notching or slurring, but all of these complexes were below 5 mm. in height. Six of the seven were involved at the peak or on the upstroke of R; the remaining one was affected at the peak of an S-wave. One other record showed a complex 10 mm. high, slurred near its base at the end of R. In three records of the entire group of thirteen, there was associated slurring in Lead III, but in all instances the deformities were either on small complexes or near the base line in one or both of the leads. In no cases were both Leads I and II involved.

Slurring or notching occurred in Lead II in nineteen instances. In five of these, however, there were deformed R-waves measuring 5 mm. or below in height, and in two there appeared small notched Q-waves at the base of moderately high R deflections. In three cases there were definite deformities at the peaks of R-waves, measuring from 9 to 13 mm. in height. Six of the remaining records showed slurring in the middle of the downstroke; two had slurring near the base of the downstroke; and one exhibited it at the base of the upstroke, all on R-waves which ranged in height from 6 to 9.5 mm.

In fourteen instances there was slurring or notching in both Leads II and III, and in three of such records the deformity was in both leads, remote from the base line, on R-waves varying from 8 to 13 mm. in height (Fig. 4). These three individuals were subjected to fluoroscopic examination and found to have hearts which were considered normal in size and contour. The other eleven records showed the deformities in one or both leads either within 2 mm. of the base line or on complexes below 5 mm. in height.

Forty-four per cent of the records presented definite slurring or notching of QRS in Lead III. Less than one-third of the involved complexes, however, were above 5 mm. in height and were affected at a point be-

yond 2 mm. from the base line. The R-wave was involved about three times as often as were Q and S together and was commonly affected at the peak or along the upstroke. Eight records showed minute triphasic "W" complexes in this lead.

Pure notching (without slurring) of the QRS deflections in Lead III was seen in 23 per cent of the records. Of this group, 47 per cent also had inverted T-waves in this lead as contrasted with 35 per cent inversion for the series as a whole. Conversely, 30 per cent of the records with inverted T-waves in Lead III also had notched QRS complexes in the same lead as compared with 23 per cent notching for the entire series. There is a slight correlation, but it is not so striking as in the series of Pardee⁴ and of Lewis.¹

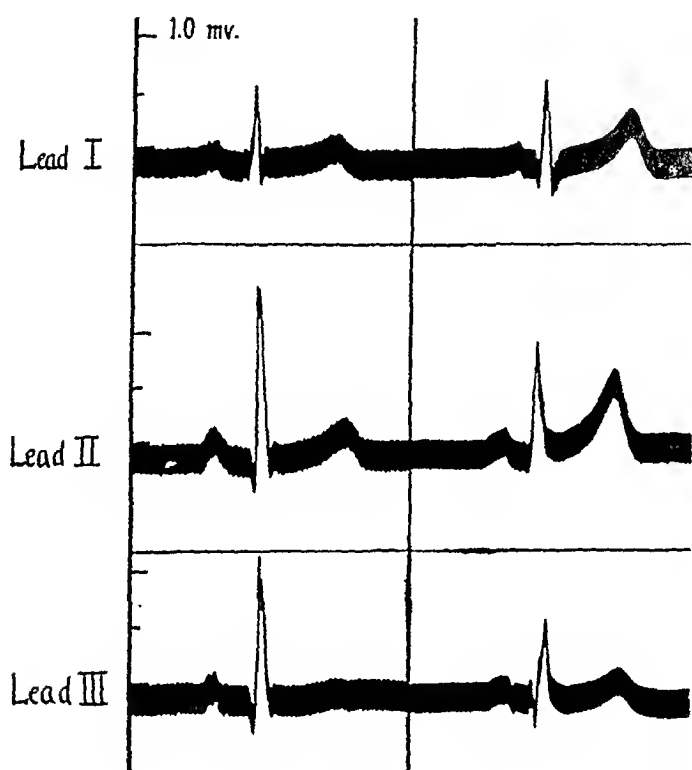


Fig. 4.—Curves from two individuals showing notching and slurring in Leads II and III.

Contrary to the findings of Katz and Kissin⁵ and of Master,⁶ slurring and notching were quite common in Lead IV, appearing there in 40 per cent of the records. The incidence and character of the deformity agreed very closely in the leg-apex lead and in the A-P lead. Eighty per cent of the involved complexes were affected along the course of the Q-wave. The small and medium-sized complexes tended to be notched rather than slurred and were involved slightly more often than the larger ones, which, if affected at all, were usually slurred. When Lead IV was involved, there was no tendency toward associated involvement of the three conventional leads. In fact, when slurring occurred in Lead IV, it was more likely than not to be absent from the three conventional leads and vice versa.

The results of this study indicate that in normal records slurring and notching are very frequent in Leads III and IV. In Lead III they commonly affect the first part of the R-wave, while in Lead IV, Q is most commonly involved. Deformations remote from the base on high complexes may occasionally be encountered in Leads II and III together. The present analysis suggests that slurring and notching do not occur in both Leads I and II or in all three leads together in normal records.

AXIS DEVIATION

It is generally considered that when the principal QRS deflections are upright in all three of the limb leads and R_2 is highest of the three, no axis deviation is present. The angle of the so-called electrical axis may be roughly calculated by measurements of the heights of the waves in any two of the three leads. The angle so determined, however, represents only the angle of the axis when the E.M.F. is at its *highest* value. There are in reality an infinite number of electrical axes corresponding to the various time components from the beginning of Q to the end of S. Aside from the major peak of E.M.F., some records present an additional secondary peak. Figure 5 is an example of a record which was found with two axes far removed from each other. These bizarre records do not fit well into any simple category.

At best, the mathematical determination of the electrical axis is only a rough approximation, but an attempt was made to calculate it in records with a simple major axis by measurement of the height of the principal QRS deflection in the two leads in which it was highest. The graph of Carter and his associates¹⁵ was used for calculation. As the axis rotates clockwise beyond $+90^\circ$, R_3 exceeds R_2 in height and the principal deflection of QRS in Lead I becomes inverted, resulting in the picture of right axis deviation. No records were found which strictly fulfilled these criteria. There were three in which the major deflection in Lead I (S-wave) was negative, but R_3 was not greater than R_2 . In two other records Lead III was greater than Lead II, but Lead I was not inverted (calculated angles of 94° and 96°).^{*} One other record was encountered in which R_2 equaled R_3 and S_1 equaled R_1 (angle of 90°). All of these six records might be considered to be on the border of right axis deviation. The most extreme "index" in the six cases calculated by the formula of White and Bock¹⁶ $(U_1 + D_3) - (D_1 + U_3)$ was -16 . The deficiencies of this formula have been pointed out.⁴ Five of these six cases of bordering right axis deviation were in males, and three of the group of six were tall, thin, narrow-chested individuals, while the remaining three were of average or slightly stocky build. There were four of the group who had x-ray plates, and only one of these had an upright type of heart.

^{*}These discrepancies are undoubtedly the result of inaccuracies in the determination of homonomous points of time which are inherent in tracings when two leads are not recorded simultaneously.

As the electrical axis passes counterclockwise beyond the $+30^\circ$ limit, R_1 becomes greater than R_2 , and the major deflection of QRS in Lead III becomes inverted. Twenty-one such cases were found and were considered representations of frank left axis deviation. In seventeen of these records the angle was between 0° and 30° , but there were four with angles measuring -8° , -24° , -71° and -104° , respectively. The only record with an "index" beyond $+20$ was the one with a -8° angle which had an "index" of $+22$.

Cases which were considered bordering on left axis deviation were as follows: Four in which R_1 equaled, but did not exceed, R_2 ; eight in which R_1 slightly exceeded R_2 , but in which the major deflection in Lead III was only small and not clearly inverted; and six in which the



Fig. 5.—A record with an electrical axis between 0° and $+90^\circ$ and another between -90° and -180° .

depth of S_3 exceeded the height of R_3 , but in which R_2 remained greater than R_1 . Analysis of the records in the latter group by measurement of voltages at approximately simultaneous time phases revealed that they showed an initial axis in the "right lower quadrant" corresponding with the initial upright peaks and a second axis in the "left upper quadrant" (deep S_3) following a counterclockwise rotation of the vectors of E.M.F. (Fig. 5).

Of the twenty-one subjects whose electrocardiograms showed left axis deviation, only five were slightly obese, and seven were of the broad-chested, pyknic type. Twelve had roentgenograms which showed a transverse position of the heart in only one case, and actually an upright heart in two others. The absence of correlation between the direction of the electrical axis and the anatomical axis is not an unexpected finding.

The influence upon the electrical axis of rotation of the heart on its longitudinal axis has been clearly shown.¹⁷ Such undemonstrable variations in rotation may entirely overshadow any tipping of the apex upward or downward.

The observation has been confirmed that the T-wave in Lead III tends to be inverted in records showing left axis deviation unassociated with heart disease.¹⁸ Fifteen of the twenty-one records with left axis deviation had inverted T-waves in Lead III (71 per cent) and of the remaining six, three had diphasic T-waves in this lead.

The combination of upright T_3 , large S_2 , and low T_1 , as reported by Proger and Minnich¹⁹ in records showing left axis deviation, was not found in any record, but two showed all of these characteristics except the low T_1 ; four had simply a deep S_2 ; and one exhibited only an upright T_3 .

THE Q-T INTERVAL

The observation that the length of the Q-T interval varies with heart rate has been made by many investigators.²⁰⁻²⁴ It has been shown, however, that the relation does not correspond to a linear function. Most of the above observers have adopted the equation $QT = K \sqrt{\text{Cycle}}$ to express the relationship although the average readings of some tended to fall more closely along the line of the function $QT = K \sqrt[3]{\text{Cycle}}$.

In the present series the Q-T interval was measured from the beginning of the initial deflection of QRS to the point where the final stroke of T just reached the base line. The average of several measurements was taken as the true figure, and these averages were tabulated both for Lead II and for that lead in which the Q-T interval was the longest. Lead II showed the longest interval in 95 per cent of instances, while the remaining 5 per cent were divided about equally between Leads I and IV. Cycle length was measured from the peaks of successive R-waves. Ordinarily an average was obtained from the eight to ten cycles in the one lead, but, if appreciable sinus arrhythmia existed, an average was obtained from the thirty or forty cycles in all four leads. It was observed that in marked sinus arrhythmia the length of the Q-T interval was often remarkably constant from cycle to cycle. This demonstrates the importance of calculating an average R-R interval in such instances, for the length of the Q-T interval apparently does not vary precisely with the wide fluctuations in cycle length.

The scatter of the readings in this series was so wide and the range of heart rates so narrow that it was impossible to construct an equation that was of any theoretical significance. It may be seen by the diagram that the general trend lies between the square root and the cube root curves (Fig. 6). For practical application it probably makes little difference which equation is adopted. When the measurements taken from Lead II were used, the average K for the closest square root function was found to be 0.397 in males and 0.415 in females, with a range be-

tween 0.337 and 0.433 for the former and between 0.380 and 0.456 for the latter. The same values obtained when the cube root function was used were average K for males 0.382, for females 0.394; limits of K in males 0.333 to 0.420, in females 0.359 to 0.432. The average values of

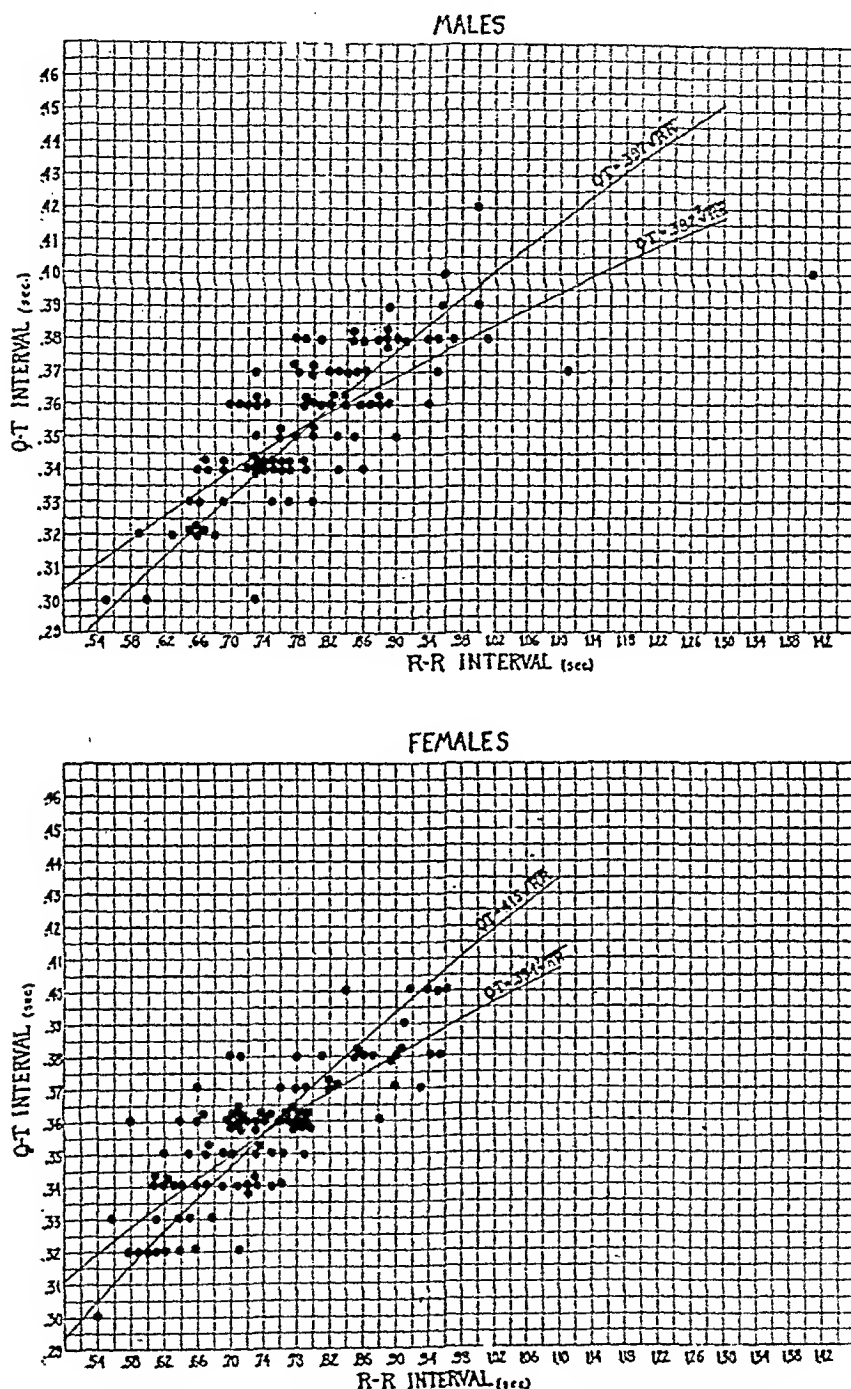


Fig. 6.—The relation of the Q-T interval to cycle length.

K determined by measurements from the lead of longest Q-T interval were all exactly 0.001 higher than the above averages from the Lead II readings.

The above values are higher than those reported by others although the existence of a sex difference has been confirmed. The rather wide

TABLE IV
ANALYSIS OF DEVIATION OF THE S-T LEVEL
(MEASUREMENTS IN MILLIMETERS)

	LEAD I			LEAD II			LEAD III			LEAD IV		
	MALES	FE- MALES	ENTIRE SERIES	MALES	FE- MALES	ENTIRE SERIES	MALES	FE- MALES	ENTIRE SERIES	MALES	FE- MALES	ENTIRE SERIES
Maximum elevation from base line	0.5	0.3	0.5	1.0	0.3	1.0	0.2	0.1	0.2	0.6	0.5	0.6
Maximum elevation from P-R level	0.7	0.3	0.7	1.3	0.5	1.3	0.5	0.2	0.5	0.6	0.5	0.6
Maximum depression from base line	0.4	0.8	0.8	0.7	1.0	1.0	0.5	0.7	0.7	2.0	1.2	2.0
Maximum depression from P-R level	0.2	0.4	0.4	0	0.3	0.3	0.3	0.5	0.5	2.0	1.2	2.0
Number showing eleva- tion from base line	12	3	15	23	3	26	6	1	7	2	2	4
Number showing eleva- tion from P-R level	34	32	66	69	45	114	23	13	36	2	2	4
Number showing depres- sion from base line	23	32	55	27	55	82	18	23	41	64	46	110
Number showing depres- sion from P-R level	3	4	7	0	5	5	3	7	10	64	48	112

variation in values of K obtained by various observers is undoubtedly due to differences in methods of measurement. One is therefore obliged to use his own series of normal controls in studying a group of pathological cases.

THE S-T LEVEL

The level between the QRS complex and the T-wave is influenced not only by ventricular events but also by the so-called auricular T-wave. The character of the latter wave is best seen in records with A-V block, where isolated P-waves may be observed. The auricular T-wave is visible as a rounded depression immediately following the P-wave. If, as stated by Sprague and White,²⁵ the wave persists for 0.34 to 0.42 second, it is evident that the S-T interval will be invaded by it and correspondingly depressed. If the wave invariably causes an S-T depression exactly equal to the P-R depression, then the P-R level should be the correct point from which to measure any superimposed ventricular deviations of the S-T level. The tendency of the auricular T-wave to begin a slope back toward the base line soon after reaching its lowest point at the bottom of the P-R level, however, introduces an error into such measurements. The usual isoelectric level of ventricular activity, therefore, probably lies about midway between the base line and the P-R level. Thus, because of the presence of the auricular T-wave, ventricular deviations measured from the P-R level will tend to be too high and those measured from the base line too low.

The various measurements of S-T deviation which were obtained are analyzed in Table IV. The point selected for measurement was the beginning of the S-T segment. Except for *elevations* of the S-T segment from the *base line* and *depressions* from the *P-R level*, which are invariably due to ventricular effect, it cannot be determined with certainty in a given instance whether auricle or ventricle is chiefly responsible for the position of the S-T segment, for its level is the result of an algebraic summation of the two effects. A more accurate indication of the part played by the ventricle may be obtained from Table V, which was constructed from 250 complexes in which the level of the S-T segment was not disturbed by the presence of an auricular T-wave. It may be seen that the segment is more often elevated than depressed, that elevations are most frequent and highest in males and in Lead II, and that depressions are most common and deepest in females and in Lead III.

In ordinary electrocardiographic practice the P-R level, because of its proximity, is usually the easiest point from which to measure the level of the S-T line. The limits of normal deviation for Leads I, II, and III by this method were 1.3 mm. above the level and 0.5 mm. below it. Measurements above 1 mm. were invariably associated with a rather deeply depressed P-R level.

It should be noted that all of the deviations measuring above 0.5 mm.

were accompanied by QRS deflections higher than 5 mm. A deviation as great as 1 mm. in a complex of low amplitude is most likely of pathological significance. It must be remembered, however, that slight deviations of the S-T level occur frequently and do not signify a diseased heart.

TABLE V
DEVIATION OF THE S-T LEVEL IN CASES WITHOUT AURICULAR T-WAVE

	LEAD I			LEAD II			LEAD III		
	MALES	FE- MALES	EN- TIRE SERIES	MALES	FE- MALES	EN- TIRE SERIES	MALES	FE- MALES	EN- TIRE SERIES
Per cent with positive deviation	17	2.5	11	25	16	22	6	1	4
Per cent with negative deviation	2	2.5	2	0	0	0	5	7	6

In Lead IV, where the auricular T-waves are usually absent, there was no appreciable discrepancy between the measurements of the S-T interval from the base line or from the P-R line. There was an exception to this in only four records with positive auricular T-waves. Elevation of S-T from either level occurred only four times; the maximum was 0.6 mm. Depression occurred in over half the records (110 times) with a maximum of -2.0 mm.

The contour of the S-T segment was also noted. It was observed that in the great majority of instances the line began a gradual slope toward the T-wave almost immediately from the end of the QRS wave or after a short level interval. Exceptions were as follows: (1) Twenty records with an upward convexity associated with an inverted T-wave in Lead III (similar to the picture seen in coronary disease in Leads I or II). (2) Ten records with a downward concavity followed by an upright T-wave. Two-thirds of these were found in Lead III. (3) Four records with an upward convexity in Lead IV followed by the usual inverted T-wave. The rounding of the S-T segment is often difficult to distinguish from a similar effect occasionally produced by the terminal portion of QRS when the latter gradually slopes toward the S-T interval as in Figure 3, A.

THE T-WAVE

In Lead I, T was always upright and of smooth contour. The same was true of the T-wave in Lead II, with the exception of two records in which it was notched and one record in which it was diphasic. In the latter record the two components measured 0.5 mm. each. When the record was repeated later, the wave was clearly upright and measured 0.5 mm. In Lead III, T was isoelectric once, diphasic thirty times, and inverted seventy times (forty-eight times in females and twenty-two times in males). All of the T-waves were inverted in the routine Lead IV and in the A-P (apex) chest lead.

A shift of the anterior chest electrode to either side of the apex affected the contour of the T-wave to a less extent than it did that of QRS, but certain variations are worthy of note. The deepest T-waves were seen in the A-P lead. When the left leg was used, the apex position gave the largest T deflection, while the smallest waves were found in the lead from the anterior axillary line. When the T-wave was shallow in the chest lead, there was occasionally a change in polarity consequent to change in position. Among thirty records in which multiple chest leads were used, there were four instances showing small inverted T-waves by the apex lead, but upright waves of the same amplitude by the fourth interspace lead.

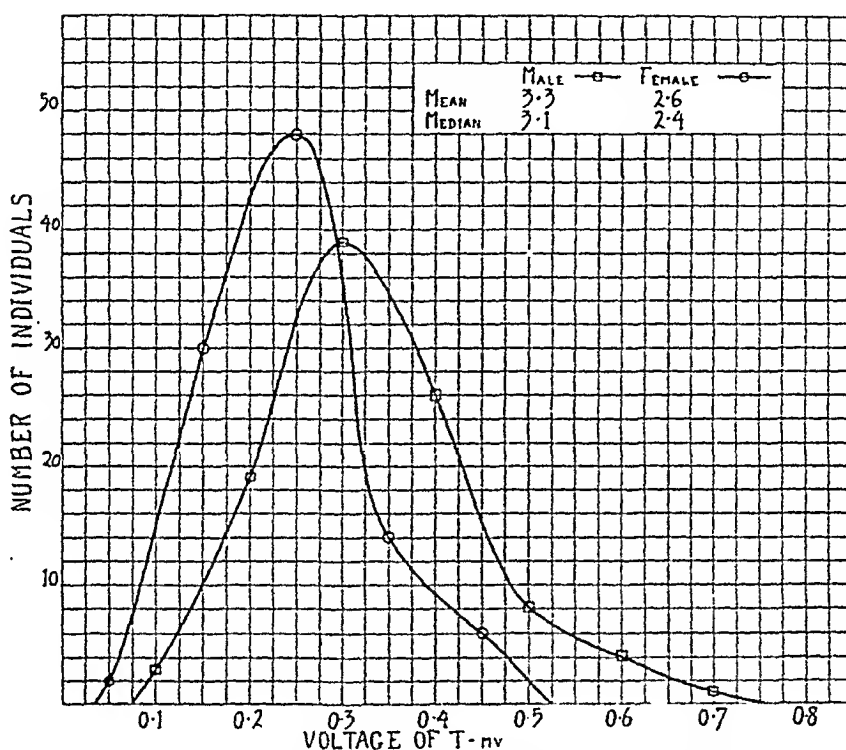


Fig. 7.—Frequency curves showing a sex difference in the voltage of the T-wave (Leads I, II, and III).

The height of the T-wave in the conventional three leads showed the same sex difference as the QRS complex (Fig. 7). Lead IV similarly showed higher values for males than for females (Table II).

ARRHYTHMIAS

An appreciable sinus arrhythmia was present in 46 per cent of the records, occurring about equally in males and in females. It was so apparent that measurement of the successive R-R intervals was unnecessary.

Two women, whose hearts were normal by roentgenographic study, exhibited a shifting pacemaker. There were two cases with occasional premature beats, one of the auricular and the other of the ventricular type.

SUMMARY

1. The maximum, minimum, and average measurements of the various wave voltages and intervals in the electrocardiograms of two hundred normal men and women have been tabulated.

2. Males showed higher voltages of QRS and of T than females, both in the conventional three leads and in the chest lead. The average amplitude of the highest QRS in Leads I, II, and III for males was 12.4 mm., for females 10.8 mm.; the average amplitude of T was 3.3 mm. for males and 2.6 mm. for females.

3. Slurring and notching of QRS were common in Leads III and IV, were occasionally seen in Leads I or II, but were not encountered in Leads I and II together or in all three limb leads.

4. Frank right axis deviation was not encountered, although approximately 10 per cent of records showed definite left axis deviation (angle less than $+30^\circ$).

5. Slight deviations of the S-T level were common. The limits of deviation measured from the P-R level were 1 mm. above this level and 0.5 mm. below in Leads I, II, and III, except in cases of a deeply depressed P-R level when the elevation sometimes slightly exceeded 1 mm. The limits of deviation in Lead IV (left leg and apex) were 0.6 mm. above the line and 2.0 mm. below.

6. There were no instances of definitely inverted or diphasic T-waves in Leads I or II, although 35 per cent of the records had inverted T-waves in Lead III. The T-wave was invariably inverted in Lead IV.

7. It cannot be said that the character of a chest lead tracing is unaffected when the posterior lead is exchanged for a lead from the left leg. The chief differences encountered when such a shift was made were changes in the polarity of the P-wave, decrease in wave voltages, and frequent departure from the simple Q-R type of QRS complex so that there was occasionally a small initial upward deflection before the usual deep downward excursion.

We wish to express our appreciation to Dr. Harold Feil for his encouragement and helpful suggestions and to Mrs. Mary Salmon Brindle and Miss Elizabeth Zschiesche for their cooperation in making the records.

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THE INITIAL VENTRICULAR DEFLECTION IN THE ELECTROCARDIOGRAMS OF NORMAL SUBJECTS*

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AS A result of several extensive electrocardiographic studies in coronary occlusion, knowledge of the diagnostic significance of the initial ventricular deflection has greatly increased in the last few years. In Lead III its importance has been recognized for a longer time than in the other leads. Many articles¹⁻¹¹ have appeared in the literature to justify Pardee's contention that the Q_3 -wave, when of such proportions as to fit his now well-known criteria,[†] is indicative of myocardial disease, although there is some difference of opinion regarding the type with which it is most frequently associated. In normal subjects, the deep Q_3 -wave as defined by these criteria, is a rarity.[‡] It is said to occur, however, with high positions of the diaphragm and consequent upward displacement of the heart as in pregnancy,^{4, 15, 16} and during deep expiration.¹

The importance of the prominent Q deflection in Leads I and II has come to light more recently. Although Fenichel and Kugell³ in 1931 suggested that a large Q-wave in these leads may have a significance similar to that of the same deflection in Lead III, it was not until two years later that Wilson and his coworkers¹⁷ demonstrated the truth of this in coronary occlusion. They called attention to the frequent association of a broad, prominent Q_1 with the T_1 changes described by Parkinson and Bedford¹⁸ that occur during the early stages of myocardial infarction. Accompanying the T_3 changes of the latter investigators, Wilson and his group have noted a large Q in Leads II and III. Electrocardiograms with these characteristics are now known as the Q_1 and the Q_3 types, respectively. The first is the result of infarction in the anterior wall, the second of infarction in the posterior wall of the heart, but exceptions occur. Barnes¹⁹ has noted similar alterations in the initial ventricular deflections in cases of coronary occlusion. From these observations it is clear that the Q-wave is of importance in all three leads both in the diagnosis and the localization of infarcts. This importance is enhanced by the fact that the abnormal Q once developed is usually permanent.

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†Pardee's criteria for the deep Q_3 are: (1) Q_3 is 25 per cent or more of the largest QRS deflection in whichever lead it may occur; (2) there is either normal or left deviation of the electrical axis; (3) curves showing an S-wave or the absence of the R-wave in Lead III are excluded. Likewise M- and W-shaped curves are excluded.

‡In the combined normal series of Lewis and Gilder¹², Cohn¹³, Master¹⁴, Pardee¹, and Edelken and Wolferth⁴ it was found twice in the electrocardiograms of 1102 young male adults including 116 normal athletes.

In an attempt to define more satisfactorily the Q_1 and Q_s electrocardiograms of Wilson, and at the same time to differentiate between these types due to coronary disease and similar ones due to other causes, Durant²⁰ has formulated certain quantitative criteria. Examination of these makes it clear that from the comparative size of the Q-waves it is possible to infer correctly in a large percentage of cases the presence of coronary occlusion. There is one difficulty, however, which Durant has admitted, namely that the criteria will eliminate certain cases of coronary disease as well as cases of noncoronary disease. It is, of course, not to be expected that any rules that may be formulated to differentiate the normal from the abnormal will hold good in all cases. Until the origin of the Q-wave is known in all cases,²¹ the ideal will be only remotely approached. In spite of these limitations a finer gauge than at present exists seems possible. To this end we have studied in detail the incidence and quantitative relationships of the Q deflection in the three leads of the electrocardiograms of normal subjects. It is hoped that these data will serve as standards with which the Q-wave in any type of heart disease may be compared.

METHOD

From an original group of 200 subjects, 22 had to be eliminated because of cardiac murmurs, persistently elevated blood pressures, or roentgenographic evidence of enlarged heart. The majority of the 178 finally selected were medical students; a small number were physicians and laboratory assistants. Of these fifteen were women. The ages varied from sixteen to thirty years. In each case a careful history was taken, and a thorough cardiac examination carried out.* All hearts were found to be roentgenographically negative although the lungs in a considerable percentage of subjects showed mild chronic changes, such as fibrosis at the roots, thickened interlobar pleura, small calcific foci, and the like. Only one case showed a well-healed, inactive, pulmonary lesion, most likely of tuberculous origin, in the right apex.

On each subject a series of five electrocardiograms† was taken, the first four of the series in the sitting position, the last in the fully recumbent position. The interval over which a series was made in any individual was approximately four weeks in more than 60 per cent of the group. The remainder, with three exceptions, were completed in thirty-two weeks or less. In one of the exceptions, the time between the first and the last tracing was a year, while in each of the other two it was thirty-two months. For the present report we have made an analysis of the first and the last curves of each series. Intermediate curves have been observed only for variations in the size of the Q deflection over a period of time. Since these variations were insignificant, no further reference to them will be made. With every electrocardiogram a simultaneous pneumogram was recorded. The pneumograph used consisted of a piece of rubber tubing containing a wire spring snugly fastened about the chest. The cavity of the tube was continuous with a recording tambour so placed in front of the camera that a downward movement in the finished record represented inspiration. The lag in this instrument was less than 0.01 second.

*The forms used to record the histories and physical examinations were those provided by the New York Heart Association, and used by the Association in the New York City Cardiac Clinics.

†A Hindle Electrocardiograph No. 1 made by Cambridge Instrument Co. was used. The string resistance was 3500 ohms.

TABLE I

The Q deflection as found in the electrocardiograms of 178 normal young adults. The table illustrates (1) incidence of normal Q; (2) mean size in tenths of a millivolt; (3) mean size expressed as a percentage of the largest QRS deflection in its own lead; (4) mean size expressed as a percentage of the largest QRS deflection in whatever lead it occurred; (5) effect of body position; (6) the effect of the phases of normal respiration; and (7) standard deviation and coefficient of variation of each mean. The means represent not a true average, but an average of those curves in which a Q occurred, as indicated by incidence.

SITTING POSITION										RECUMBENT POSITION									
Q		Q PERCENT. OF LARG-EST QRS DEFLECTION IN ITS OWN LEAD				Q PERCENT. OF LARG-EST QRS DEFLECTION IN ALL THREE LEADS				Q		Q PERCENT. OF LARG-EST QRS DEFLECTION IN ITS OWN LEAD				Q PERCENT. OF LARG-EST QRS DEFLECTION IN ALL THREE LEADS			
TENTHS OF A MILLI-VOLT	STAND. DEV.	COEFF. VAR.	PER CENT	STAND. DEV.	COEFF. VAR.	PER CENT	STAND. DEV.	COEFF. VAR.	TENTHS OF A MILLI-VOLT	STAND. DEV.	COEFF. VAR.	PER CENT	STAND. DEV.	COEFF. VAR.	PER CENT	STAND. DEV.	COEFF. VAR.		
Lead I																			
1.09	0.73	66.9	10.1	6.3	62.4	7.6	5.8	76.3	0.91	0.57	62.6	11.1	6.0	54.0	6.7	4.3	64.1		
		67 cases or 37.0%									74 cases or 41.6%								
1.08	0.72	66.6	9.7	5.8	59.8	7.6	4.9	64.4	0.91	0.58	63.7	10.3	6.0	58.3	6.5	4.1	63.0		
		69 cases or 38.8%									76 cases or 42.7%								
Lead II																			
1.18	0.77	65.1	7.4	4.2	56.7	7.3	4.2	57.6	1.30	0.83	63.8	7.7	4.3	55.8	7.6	4.1	53.9		
		116 cases or 65.2%									118 cases or 66.3%								
1.23	0.80	65.0	7.4	4.1	55.4	7.2	3.7	51.4	1.30	0.83	63.8	7.6	4.2	55.2	7.4	4.0	54.0		
		115 cases or 64.7%									119 cases or 66.9%								
Lead III																			
1.58	1.00	63.3	16.5	14.4	87.2	10.5	5.1	48.6	1.42	0.90	63.4	12.3	8.6	69.9	8.3	4.9	59.0		
		109 cases or 61.3%									112 cases or 63.0%								
1.67	1.12	67.1	17.5	16.2	90.5	10.6	5.2	49.1	1.45	1.00	68.9	12.3	9.1	73.9	8.3	4.6	55.4		
		108 cases or 60.7%									111 cases or 62.4%								

We have named any initial downward movement of the string shadow Q regardless of the nature of the remainder of the ventricular deflections. The absolute size of the Q-waves in the various phases of respiration and with the subject in both the sitting and recumbent positions was determined and corrected, if standardization of the instrument was erroneous. The largest QRS deflection in each lead was also noted.

RESULTS

Some of the electrocardiograms in this series were not within the normal limits, as these are now generally accepted. Several showed high voltage (largest QRS deflection over 2.0 millivolts). Only one showed a QRS duration greater than 0.1 second. There were 29 with left axis deviation or tendency to left axis deviation. Of these, only 5 showed a negative angle alpha calculated by the method of Carter, Richter, and Greene.²² There were 17 instances of right axis deviation or tendency to right axis deviation. The maximum angle alpha of these was +107 degrees found during normal respiration with the subject in the sitting position. These and other unusual findings in electrocardiograms of normal persons will be taken up in greater detail in a subsequent paper. Since each individual was carefully studied physically and roentgenographically, it is felt that the group may be justly considered an adequate random sample of normal, young adults.

Incidence of the Normal Q Deflection.—Table I shows, in addition to other data, the incidence of the Q in the three leads during normal respiration, with the subject in both the sitting and the recumbent positions. The occurrence of Q may be simply restated as follows: In any ten normal electrocardiograms a Q deflection may be expected in Lead I approximately four times, and in Lead II or Lead III slightly more than six times. In all leads these figures are somewhat higher for the recumbent than for the sitting position of the subject. They are not affected a great deal by the phases of normal respiration.

Closer examination reveals that these data are inadequate since they tell one nothing about the frequency of Q in any combination of leads, or in any one lead to the exclusion of the others. Table II gives these details. In compiling it, we regarded a Q-wave as present if seen in inspiration, expiration, or both. It is obvious that Q is most commonly found in Leads II and III together (69 instances, or 38.7 per cent sitting, and 66 instances, or 37.1 per cent recumbent). This is the combination to which much pathological significance is attached, more especially when it is associated with RS-T segment and T-wave changes in these leads.^{17, 19, 20, 23} In this series RS-T displacement was never great, and no inverted T-waves were found in Leads I or II. However, an inverted T₃-wave was present in 46 instances. In 22 of these a Q₂ and a Q₃ were present when the subject was sitting, and in 9 when the subject was reclining. Since this combination occurs normally, there is obviously a need for a strict quantitative set of standards for distinguishing the normal from the abnormal.

TABLE II

Incidence of the Q deflection during normal respiration in each lead and in combinations of the three leads. In compiling this table, we regarded a Q-wave as present if seen in either or both phases of normal respiration.

		NO Q IN ANY LEAD	LEAD I ONLY	LEAD II ONLY	LEAD III ONLY	LEADS I AND II	LEADS I AND III	LEADS II AND III	LEADS I, II, AND III	TO- TALS
Sitting	Cases	19	23	4	16	16	2	69	29	178
	Per cent total	10.7%	12.9%	2.2%	9.0%	9.0%	1.2%	38.7%	16.3%	100%
Recum- bent	Cases	16	26	5	14	13	3	66	35	178
	Per cent total	9.0%	14.6%	2.8%	7.9%	7.3%	1.7%	37.1%	19.6%	100%

Referring to Table II again it will be noted that the least common combination was a Q-wave in Leads I and III. Not an inconsiderable number of subjects (23, or 12.9 per cent, sitting and 26, or 14.6 per cent, recumbent) showed this deflection in Lead I only.

TABLE III

A comparison of the present normal series with that of Lewis and Gilder. Minimum, maximum, and mean Q's are given in tenths of a millivolt. (See text for explanation of high maxima in present series.)

LEAD	LEWIS AND GILDER 52 NORMALS			PRESENT SERIES 178 NORMALS				MEAN OF INSP. AND EXP.
	MIN.	MAX.	MEAN		MIN.	MAX.	MEAN	
I	0	2.0	0.51	Insp.	0	4.0	0.41	0.42
				Exp.	0	4.0	0.42	
II	0	2.5	0.73	Insp.	0	4.0	0.77	0.78
				Exp.	0	5.0	0.79	
III	0	2.5	0.86	Insp.	0	6.0	0.98	1.00
				Exp.	0	7.0	1.02	

Size of the Normal Q Deflection.—Table III shows how the mean values of Q obtained from this series of 178 compares with similar values obtained by Lewis and Gilder in 52 normal subjects. Since the latter study was carried out with the subjects in the sitting position, values obtained similarly in this study are given. The two series are not strictly comparable, however, since we have studied electrocardiograms of physically and roentgenographically normal adults, while Lewis and Gilder eliminated one case from their series on electrocardiographic grounds only. The greatest difference between the two is seen in the maximum Q-waves obtained. The number of these deflections in the present series that exceeded the maxima of Lewis in either phase of normal respiration were four in Lead I, five in Lead II, and seventeen in Lead III. The four exceptions showed a tendency to high voltage (largest QRS deflection greater than 1.9 millivolts) in Lead I, Lead II, or both. Of the five exceptions in Lead II, four also showed high voltage. The other (Case 128) displayed right axis deviation

with an angle alpha of +107 degrees. In Lead III of the seventeen exceeding Lewis' maximum of 0.25 millivolt, there were eleven with a Q-wave depth of 0.3 millivolt, almost all of which showed no other unusual electrocardiographic features. The remaining six, with an initial downward deflection varying in size from 0.35 to 0.7 millivolt, showed in every instance some electrocardiographic peculiarity. There were three with R-waves exceeding 2.0 millivolts, two with right axis deviation or a tendency to it (angle alpha +107 degrees and +77 degrees respectively), and one (Case 101) with a deep initial deflection in expiration only. In the last an upward movement of considerable size preceded the downward movement of the string during normal inspiration.

The unusually large Q-waves in the tracings discussed greatly influence the mean values given in Table III. If all those exceeding Lewis' maxima are eliminated, the means for both phases of respiration given in the table become:

Lead I—0.37; Lead II—0.71; Lead III—0.86.

In Leads II and III these are almost identical with similar figures given by Lewis and Gilder. In Lead I, however, the mean size of Q is much lower in this series.

Table I gives perhaps a better conception of the size of the average Q-wave in this group of 178 subjects, since the means given there were calculated only from those curves, indicated by incidence, that showed this deflection. In each lead, four values of Q were obtained from its occurrence during normal inspiration and normal expiration with the subject in both the sitting and recumbent positions. Normal respiration had little effect on the mean size of Q. In only a few instances (usually in Lead III) did this deflection vary by as much as 0.1 millivolt during quiet breathing, and in over 90 per cent of curves showing a Q-wave it did not vary at all. On the other hand, position of the body had effects as shown. In individual curves, variations caused by recumbency did not exceed 0.1 millivolt in Leads I or II. Greater changes than this did occur in Lead III, however. The number of Q-waves that were increased, decreased, or unaffected by the supine position of the subject were evenly divided so that in any lead during normal inspiration or expiration approximately one-third fell under each of these three classes.

The standard deviations and the coefficients of variation given in Table I indicate the dispersion of the variates. Obviously these and the means of absolute Q size would be reduced somewhat by omitting curves exhibiting right axis deviation or high voltage.

Normal Q-Wave Expressed as a Percentage of Other QRS Deflections.—The size of each Q-wave was calculated in terms of the largest QRS deflection in its own lead, and of the largest QRS deflection in whatever lead it occurred. The mean values of each of these in percentages

are given in Table I with the standard deviations and coefficients of variation. The great variability of Q_3 expressed as a percentage of other Lead III deflections with the subject in a sitting position is evident from the standard deviations and the coefficients of variation. This is a natural corollary of the great variability of the normal initial ventricular deflections seen in Lead III.

Maxima of Absolute and Relative Q Size.—From the data thus far presented we have set down certain maxima of absolute and relative size of the normal Q-wave that may be used as criteria. These were determined from the frequency tables constructed for the calculation of the various statistical constants, and are presented in Table V. There were nineteen subjects with curves that exceeded one or more of the maximum values given. Of these, however, twelve showed either an R-wave in one or more leads exceeding 1.9 millivolts, or a tendency to right axis deviation (angle alpha greater than + 75 degrees). As would be expected, those with the latter peculiarity exceeded the maxima in Lead III, or Leads II and III. The remaining seven subjects are indicated in Table V. Their case numbers have been placed under those maxima which their curves exceeded. Some remarks on

TABLE IV

The Q deflection as found in electrocardiograms of 178 normal young adults during forced inspiration and expiration. This table is in every respect like Table I except that the standard deviations and coefficients of variation have been omitted.

	SITTING POSITION			RECUMBENT POSITION		
	Q IN TENTHS OF A MILLIVOLT	Q PER- CENTAGE OF LARGEST QRS DE- FLECTION IN ITS OWN LEAD	Q PER- CENTAGE OF LARGEST QRS DE- FLECTION IN ALL THREE LEADS	Q IN TENTHS OF A MILLIVOLT	Q PER- CENTAGE OF LARGEST QRS DE- FLECTION IN ITS OWN LEAD	Q PER- CENTAGE OF LARGEST QRS DE- FLECTION IN ALL THREE LEADS
<i>Lead I</i>						
Deep insp.	0.87	11.3	6.5	0.80	12.5	6.0
	60 cases or 33.8%			69 cases or 38.8%		
Deep exp.	0.99	10.2	7.3	0.89	11.0	6.4
	65 cases or 36.6%			71 cases or 39.9%		
<i>Lead II</i>						
Deep insp.	1.13	6.9	6.5	1.19	6.9	6.8
	108 cases or 60.7%			109 cases or 61.3%		
Deep exp.	1.23	7.4	7.3	1.30	7.4	7.3
	114 cases or 64.1%			118 cases or 66.2%		
<i>Lead III</i>						
Deep insp.	1.32	10.6	8.3	1.26	9.7	7.4
	106 cases or 59.5%			102 cases or 57.3%		
Deep exp.	1.62	17.0	10.6	1.43	11.4	8.2
	109 cases or 61.3%			111 cases or 62.4%		

them seem necessary. Subject 161 showed an R_2 of 1.9 millivolts in the sitting position which decreased to 1.6 millivolts with recumbency. Q_1 was 0.4 millivolt and 0.3 millivolt with the subject sitting and reclining, respectively. Since the criteria are not applicable to high voltage curves, this Q exceeded the maximum of *absolute* size only when the subject was recumbent. This is the only undisputed instance in which this was true, for, as previously noted, the electrocardiograms of subject 101 showed a deep initial downward movement of the string shadow during normal expiration only. Subjects 104 and 223 had low, vibratory complexes in Lead III. The remaining three (subjects 32, 113, 174) showed no electrocardiographic peculiarities. It will be noted that the last five mentioned exceeded the maxima of *relative* Q size only. It is clear from the table and discussion that Q_3 expressed as a percentage of the highest ventricular deflection in Lead III is a difficult normal to define, and is not as valuable a measurement as Q_3 expressed as a percentage of the largest QRS deflection in all three leads.

No curve in this series displayed a Q_3 that exceeded Pardee's criteria for the maximum normal size of this deflection.

Effect of Deep Respiration on the Normal Q Deflection.—The effects of deep respiration on the normal Q -wave are summarized in Tables IV, VI, and VII. Table IV is similar to Table I except that the standard deviations and the coefficients of variations have been omitted.

TABLE VI

Number and percentage of total Q -waves seen during normal inspiration that were increased, decreased, or unaffected by deep inspiration.

LEAD	SITTING POSITION				RECUMBENT POSITION			
	IN- CREASED	DE- CREASED	SAME	TOTAL*	IN- CREASED	DE- CREASED	SAME	TOTAL*
I	3 4.3%	32 46.4%	34 49.3%	69 100%	5 6.6%	29 38.2%	42 55.2%	76 100%
II	13 10.9%	47 39.5%	59 49.6%	119 100%	11 9.1%	45 37.2%	65 53.7%	121 100%
III	18 15.6%	54 47.0%	43 37.4%	115 100%	9 7.8%	45 38.8%	62 53.4%	116 100%

The statement that a high position of the diaphragm as in deep expiration tends to increase the size of Q_3 was true in almost 50 per cent of the electrocardiograms taken with the subject sitting, if the comparison was made with the size of the wave during deep inspiration. Approximately 10 per cent were smaller, and the remainder unaffected. With the subject reclining, only 35 per cent were larger during deep expiration. When, on the other hand, Q size during normal expiration was used as a point of comparison, deep expiration affected the Q -wave as seen in Table VII. It shows that less than 25 per cent were increased when the subject was sitting, and only 12.4 per cent when the subject was reclining.

TABLE VII

Number and percentage of total Q-waves seen during normal expiration that were increased, decreased, or unaffected by deep expiration.

LEAD	SITTING POSITION				RECUMBENT POSITION			
	IN- CREASED	DE- CREASED	SAME	TOTAL*	IN- CREASED	DE- CREASED	SAME	TOTAL*
I	8 11.1%	25 34.7%	39 54.2%	72 100%	8 10.3%	20 25.6%	50 64.1%	78 100%
II	28 23.5%	29 24.3%	62 52.2%	119 100%	14 11.5%	17 13.9%	91 74.6%	122 100%
III	25 22.5%	30 27.3%	56 50.2%	111 100%	14 12.4%	16 14.2%	83 73.4%	113 100%

*The totals in Tables VI and VII differ from those given for incidence in Tables I and IV because in a few instances in each lead, a Q-wave not present during normal respiration was present during deep respiration. The reverse was also true in a few cases.

SUMMARY

1. Electrocardiograms of 178 young normal adults were taken with the subjects in both the sitting and the fully recumbent positions. Simultaneous pneumograms were recorded.

2. The incidence and the absolute and relative size of the Q-waves were determined. The effects of body position and the phases of normal and forced respiration on these were studied.

3. In either the sitting or recumbent position of the subject, and during either phase of normal respiration approximately 40 per cent of the electrocardiograms showed a Q-wave in Lead I, and 60 per cent in Lead II or in Lead III. Slightly less than 40 per cent showed a Q-wave in Lead II and in Lead III.

4. In either the sitting or recumbent position of the subject, and during either phase of normal respiration the maximum, normal Q was 0.2 millivolt in Lead I, 0.25 millivolt in Lead II, and 0.3 millivolt in Lead III. The maximum normal Q expressed as a percentage of the highest QRS deflection in whatever lead it occurred was 15 per cent in Lead I, 20 per cent in Lead II, and 25 per cent in Lead III. The maximum normal Q expressed as a percentage of the highest QRS deflection in its own lead was 20 per cent in Lead I, 15 per cent in Lead II, and 50 per cent in Lead III. The last was reduced by recumbency to 30 per cent.

5. These maxima did not hold for any lead if an R-wave of 1.9 millivolts or more was present. They did not hold for Leads II and III if there was right axis deviation or an angle alpha greater than + 75 degrees.

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THE CLINICAL DIAGNOSIS OF TRICUSPID STENOSIS

REPORT OF A CASE COMPLICATED BY PAROXYSMAL NODAL TACHYCARDIA AND A-V DISSOCIATION*

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ACQUIRED tricuspid stenosis is rarely diagnosed ante mortem. Zeisler¹ states that a review of the world literature to 1933 reveals only 250 such cases, the correct diagnosis having been made ante mortem in only 31 cases. Such an uncommon cardiac lesion, once suspected, is of particular interest to the cardiologist if for no other reason than from the standpoint of diagnostic acumen.

The earlier discussions on this subject were somewhat equivocal and stressed the deceptiveness of the symptoms and physical signs. Later reports of verified cases, however, have been more explicit. The almost invariable association of this lesion with mitral stenosis complicates its detection. The relative tricuspid insufficiency that frequently occurs with mitral stenosis may present temporarily a confusing picture, yet tricuspid incompetency has been shown by Kerr and Warren² to be a very common finding in heart failure and should be easily recognized and correctly diagnosed. In several rare instances, pericardial effusion and adhesive pericarditis have been described as simulating tricuspid stenosis.³ However, when such complicating factors are reasonably ruled out by various diagnostic methods, the pathological physiology associated with tricuspid stenosis has been found to produce the following clinical manifestations:

1. Dyspnea on exertion, practically always present and usually out of proportion to that observed in mitral stenosis.

2. Cyanosis of varying degree, often marked.

3. Distention of the cervical and brachial veins, with presystolic pulsations or large "a" waves in the phlebogram. In some instances, combined inspection of the apex beat and jugular pulse may show the exaggerated wave to be synchronous with contraction of the auricles, even without the aid of instruments.

4. Enlargement of the liver, with auricular pulsations detectable either by palpation or with the aid of hepatic pulse tracings. Double hepatic pulsations may be explained on the basis of an hypertrophied right auricle with hindrance to the ejection of blood into the right ventricle. According to Young,⁴ the most valuable clinical sign of

*From the Department of Medicine, University of California Medical School, San Francisco. This case report, slightly modified since, appeared in *Medical Papers* dedicated to Dr. Henry A. Christian, February 16, 1936, published by the Waverly Press, Baltimore, Md.

organic tricuspid disease is the presence of a pulsating liver which continues to pulsate under measures designed to effect the cessation of this phenomenon.

5. A diastolic or presystolic murmur over the xiphoid end of the sternum differing in quality, and sometimes, although not necessarily, in timing, from a similar murmur at the apical region due to associated mitral stenosis. The systolic murmur due to the invariably associated tricuspid regurgitation is less easily differentiated from that at the apex, as a rule.

6. Enlargement of the heart to the right, with dilatation or hypertrophy of the right auricle.

7. Disappearance of the peripheral signs dependent upon auricular activity during auricular fibrillation, auricular arrest, nodal rhythm, or tachycardia.

It would seem that when a patient with chronic rheumatic heart disease and mitral stenosis presents the previously described findings, a clinical diagnosis of organic tricuspid stenosis is justified. Upon this assumption, the following case history is presented:

E. T., No. 82,380-M, a married white woman, twenty-four years old, first entered the University of California Hospital on the Medical Service, March 29, 1935, complaining of dyspnea on moderate exertion since the age of nine years and rapid heart action of five days' duration. She had had chorea at the age of seven years, for which she was confined to bed for three months, but no history was elicited that was suggestive of acute rheumatic fever. She had always been considered a delicate child; had had measles twice, at the ages of four and ten years, and chicken-pox at the age of 13; and her tonsils had been removed when she was four years old. About two years after her recovery from chorea, she had first noticed her inability to run or play as other children did, because of shortness of breath and "pounding" of her heart. Ascent of one flight of stairs always "left her puffing."

She married at the age of seventeen years, and one year later was delivered of a normal male infant without complications at seven months. The following year she was delivered of a full-term female infant, this time again without difficulty. In the succeeding two years she had two spontaneous abortions, each following two months of pregnancy. Seven months after the last abortion, a seven months' pregnancy was complicated by hemorrhage, and a dead baby was delivered with forceps. Her recovery from this mishap was associated with weakness for several months but was otherwise uneventful. It is of interest that she was no more dyspneic than usual during all of these pregnancies, and that she nursed each of the first two children for six months following birth.

During the second pregnancy, in November, 1930, she had her first "heart attack," characterized by the sudden onset of a rapid heart rate and palpitation, which ceased abruptly after several hours. A similar episode occurred six months later, and from then on she began to have attacks of longer duration and at more frequent intervals. During the year preceding her hospital entry, the attacks occurred about once a week, lasting from twelve to twenty-four hours. The symptoms associated with these attacks were marked dyspnea, a feeling of fullness in the neck, and rapid pounding of the heart, but no orthopnea. She stated that she was more comfortable lying on one side or prone. The episodes usually terminated with nausea and vomiting, which was not induced. She had never tried any of the usual procedures known to produce a cessation of paroxysmal auricular tachycardia. She had

had no edema of the ankles. About two months before she entered the hospital, she was bothered by a hacking cough productive daily of about one cupful of heavy, yellowish sputum which was occasionally blood streaked. At the time of onset of the cough, which was usually worse at night, she began to find it necessary to use two pillows in order to sleep comfortably. Following the appearance of these symptoms she lost about 15 pounds in weight.

She was first seen in the Out-Patient Department on Aug. 13, 1931. A diagnosis of mitral stenosis and insufficiency was made, and she was advised to take digitalis in small doses. She was not seen again in the clinic until Nov. 26, 1934, and at this time digitalis was again prescribed. On Dec. 7, 1934, she again reported complaining of nausea and vomiting, and her pulse was described at that time as irregular. Medication was discontinued for four days, and then resumed in 0.1 gm. doses daily. She was seen at fairly regular intervals until March 29, 1935, when she appeared at the clinic with the complaint of a rapid heart rate of five days' duration,

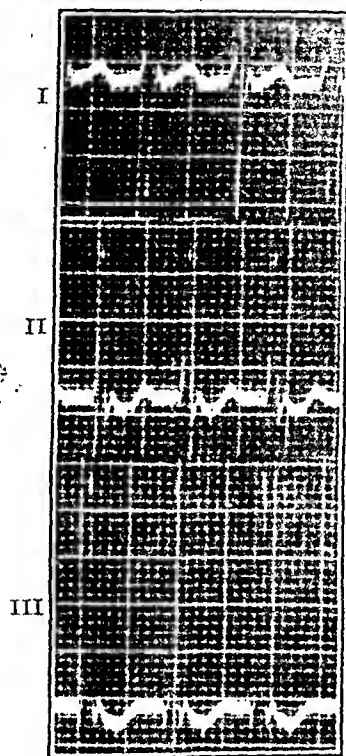


Fig. 1.—Electrocardiogram taken March 29, 1935, showing nodal tachycardia, right ventricular preponderance, with a rate of 168 per minute and regular rhythm.

associated on several occasions with nausea and vomiting, constant, dull, aching pain in the epigastrium, and intermittent sharp substernal pains of very short duration radiating through to the back between the shoulder blades. She was referred immediately to the hospital where the following clinical picture was noted:

The patient was a pale, undernourished young woman of slender build, rather nervous, and breathing rapidly. She seemed more comfortable lying prone or on one side. The fingers, toes, lips, nose, and ears were cyanotic. There was no edema or ascites. The fingers showed slight clubbing. The cervical and brachial veins were markedly distended and pulsating regularly. The lungs were clear. A pre-systolic thrill was palpable at the apical region. The heart was found by percussion to be enlarged both to the right and left; the right border of dullness in the fifth intercostal space was 5 cm., and the left border of dullness in the same intercostal space was 11.5 cm. from the midsternal line. On auscultation a loud to-and-fro murmur was audible over the entire precordium, of maximum intensity at the

apex. The cardiac rhythm was regular, and the rate 164 per minute. The blood pressure was not obtainable by the auscultatory method; the systolic reading by palpation was 85. The smooth, blunt, tender edge of the liver was palpable 7.5 cm. below the right costal margin. Marked systolic pulsations were palpable, synchronous with the radial pulse. The tentative diagnosis made at this time was mitral stenosis and insufficiency, relative tricuspid insufficiency, and paroxysmal auricular tachycardia. Carotid sinus and ocular pressure were without effect upon the rapid rate.

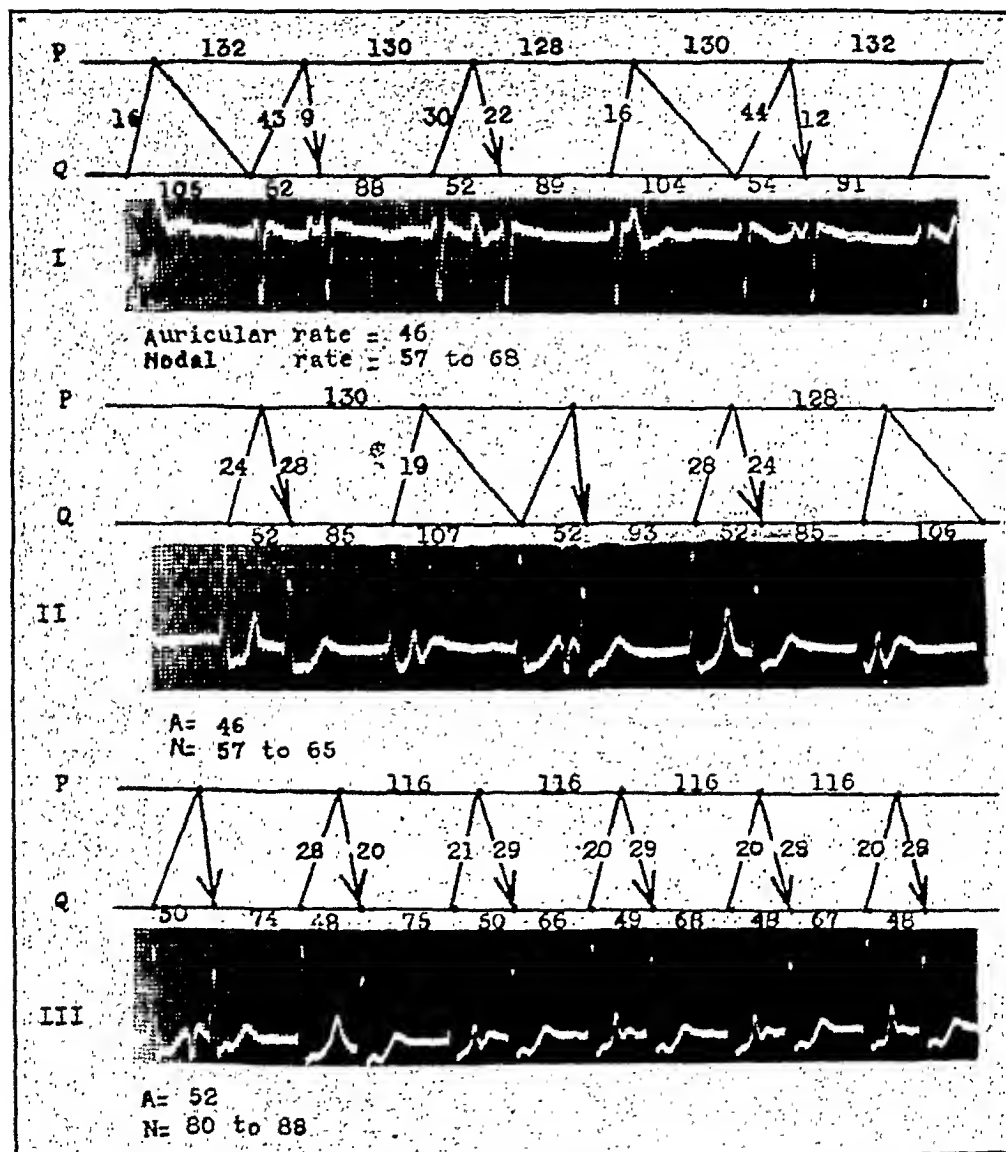


Fig. 2.—Electrocardiogram taken April 1, 1935, showing A-V dissociation undoubtedly due to digitalis. The following analysis of these curves was made by Dr. E. B. Zeisler of Chicago, Ill.:

"In Lead I there is a slight sinus arrhythmia, the rate averaging 46. There is a nodal arrhythmia, the rate varying from 57 to 68. The P-Q segments marked with an arrow represent conduction. There are three conducted impulses, the others being adventitiously blocked because their preceding recovery period, RP, is too short. The situation is similar in Lead II.

"In Lead III the difference between the nodal and sinus rates is sufficiently great so that every auricular impulse is conducted to the ventricles; consequently every second ventricular impulse is conducted from the auricles, while the other ventricular impulses originate in the A-V node. In this lead there is no adventitious block.

"It may be noted that the P-Q conduction interval varies inversely as the preceding recovery period, RP, as is to be expected. The slight variation in this correspondence is due to variability in A-V conductivity."

An electrocardiogram showed the tachycardia to be of nodal origin (Fig. 1). Laboratory tests, including the Wassermann reaction, were negative.

The patient was given 0.8 gm. of digitalis folia within eight hours, by the end of which time the cardiac rate had temporarily slowed to 80 per minute. By the end of fourteen hours she had received 1.2 gm. of digitalis; the rate, however, had risen to 150 per minute. Electrocardiograms taken at this time were similar to those in Fig. 1. The administration of digitalis was then discontinued, and quinidine sulphate was given beginning at 2:00 P.M. on March 30, 1935. After two doses of 0.2 gm. quinidine sulphate at two-hour intervals, the rate dropped to 85 per minute; the rhythm was regular. The dosage of quinidine, given every three hours during the day and night, remained the same until April 1, 1935, when it was increased to 0.4 gm. three times daily.

Examination of the heart while its rate was slow and the rhythm regular afforded a better opportunity to determine the character of the cardiac murmurs. A loud,

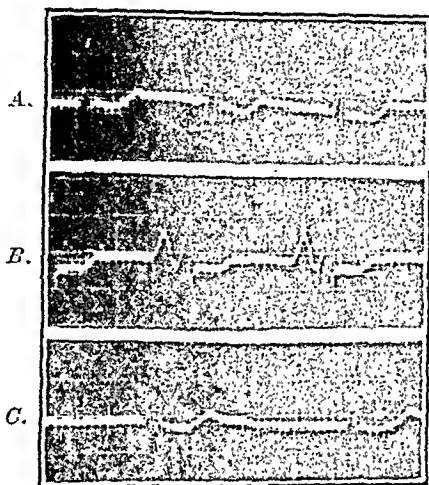


Fig. 3.—Electrocardiogram (Lead II) taken April 5, 1935, showing the transitions from nodal to normal sinus rhythm with change in posture. A, 2:15 P.M., after moderate exercise; B, 2:30 P.M., while sitting up; C, 3:00 P.M., after rest—lying down.

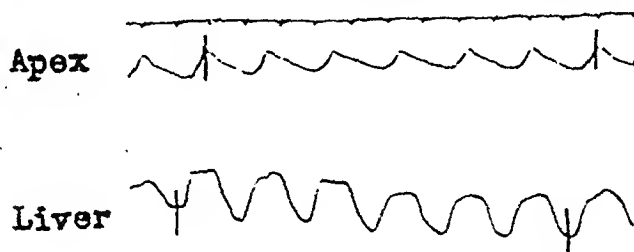


Fig. 4.—Simultaneous tracings of the apical impulse and systolic pulsations in the liver during nodal tachycardia; taken April 11, 1935. The maximal apical impulse precedes the maximal hepatic impulse by approximately 0.1 second. The rhythm is regular, the rate 168 per minute. The time marker was calibrated for 0.2 second.

long, low-pitched diastolic rumble terminating in a short, presystolic accentuation was audible at the apex. Over the lower portion of the sternum, it was possible to detect a well-localized, short, high-pitched diastolic murmur. This diastolic murmur over the tricuspid region was different, in pitch and timing, from that heard at the apex, and there was no audible presystolic element; it was distinctly well localized to a small region over the xiphoid end of the sternum. The systolic murmurs heard in both regions were similar in timing, that at the tricuspid region being closer to the ear and somewhat more blowing in character than the loud, systolic bruit heard at the apex. The pulmonic second sound was markedly accentuated. The blood pressure was 110/78, and the venous pressure by the direct method, 26 cm. of water.

On April 1, 1935, the patient was found to have an arrhythmia which was attributed to the toxic effects of digitalis. An electrocardiogram taken at this time (Fig. 2) showed auriculoventricular dissociation⁵ of the interference-dissociation type of Mobitz. In other words the A-V dissociation was due entirely to the fact that the nodal rate was greater than the sinus rate without any essential A-V block, the A-V block in the tracings being entirely adventitious.

Fluoroscopic examination and films of the chest taken April 2, 1935, showed a general enlargement of the heart and a considerable amount of pulmonary congestion. During fluoroscopy in the left anterior oblique position, the shadow due to the right auricle appeared to be elevated and somewhat acutely angulated. The left auricle, viewed in the right posterior oblique position, likewise appeared enlarged.

The administration of quinidine sulphate was continued until April 5, 1935, when an electrocardiogram (Fig. 3) showed the transition from nodal to normal rhythm occurring when the patient's posture was changed from the supine to the erect.

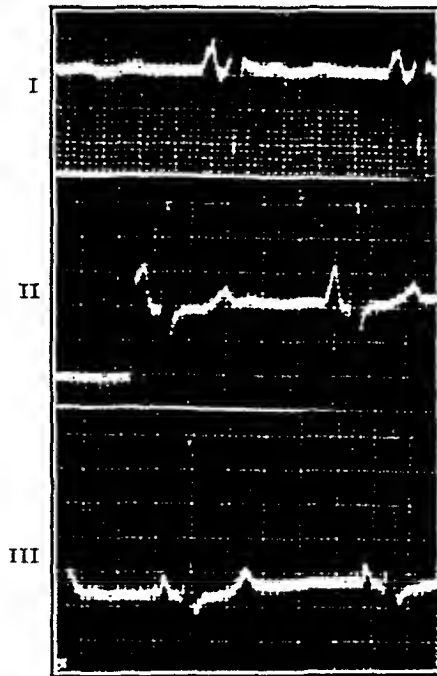


Fig. 5.—Electrocardiogram taken April 12, 1935, showing a right ventricular preponderance, large P-waves in Leads I and II, with notching in P_1 .

Administration of the drug was temporarily discontinued, and the rhythm reverted to normal on April 8, 1935. The patient felt so well that she was then allowed to be up and around for several days. On April 11, 1935, she had another attack of nodal tachycardia, with a cardiac rate of 168 and regular rhythm. Hepatic pulse tracings (Fig. 4) demonstrated the forceful systolic pulsations which were so plainly palpable at this time. On April 12, 1935, the patient was given 1.2 gm. of quinidine sulphate over a period of seven hours, at the end of which time the rate dropped to 72 per minute. It was at this time that pronounced double pulsations were first noticed in the liver. An electrocardiogram showed large P-waves and a right ventricular preponderance; the rate and rhythm were normal (Fig. 5). Tracings were obtained exhibiting the well-developed auricular and ventricular pulsations in the liver (Fig. 6). The "a" wave in the jugular tracing was practically synchronous with the auricular pulsation of the liver. The onset of the auricular deflection in the liver preceded the same point on the radial tracing by 0.22 second, and likewise preceded the onset of systole by slightly more than 0.2 second.

The condition of the patient was greatly improved when she was discharged from the hospital on April 12, 1935. She was directed to take quinidine sulphate, 0.2 gm. three times daily. On April 22, 1935, she had an attack of tachycardia during the night, lasting about eight hours, and on April 26 a similar attack lasting about six hours. The dosage of quinidine was increased to 0.2 gm. four times daily, and the patient has had no similar episodes since.

Electrophonocardiograms taken on May 22, 1935, were of considerable value in depicting graphically the difference in the murmurs. A tracing obtained with the microphone at the apex showed the presence of a long presystolic murmur and a total systolic murmur (Fig. 7), with accentuation in midsystole. There was no sharp second sound. It had been replaced by a diastolic murmur approximately

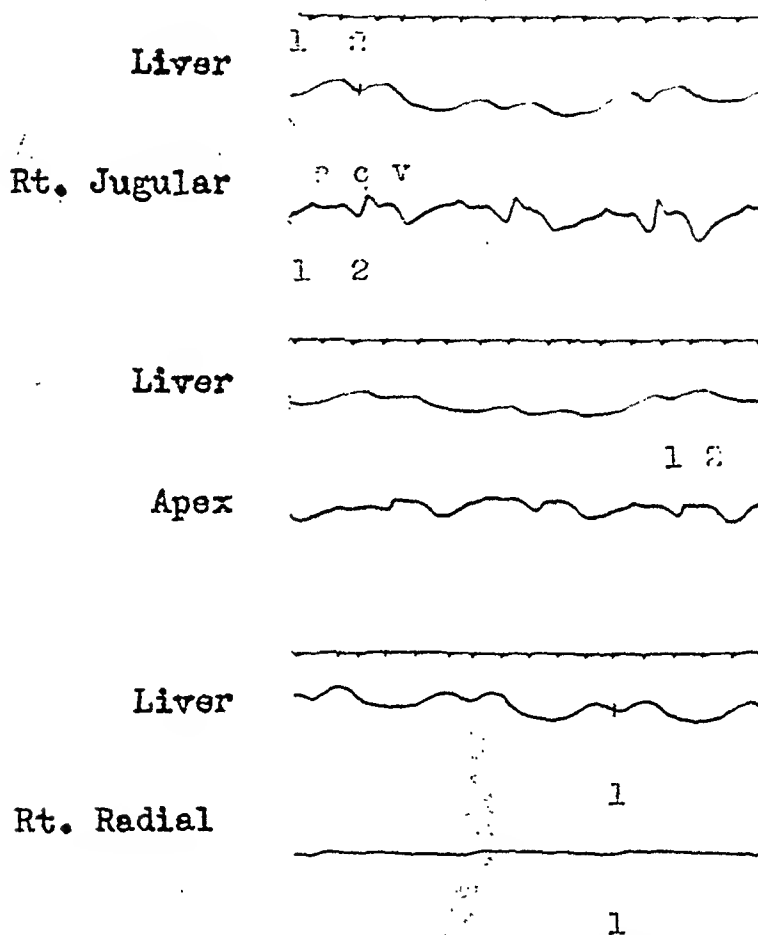


Fig. 6.—Tracings obtained April 12, 1935, showing auricular and ventricular pulsations in the liver taken simultaneously with the right jugular pulsations, apical impulse, and right radial pulse during regular sinus rhythm. The time marker was calibrated for 0.2 second.

three times the duration of a normal second sound. The tracing taken with the microphone over the xiphoid end of the sternum (Fig. 8) presented a definite contrast, with little, if any, presystolic oscillation. The accentuation of the systolic murmur occurred somewhat earlier in systole. The diastolic murmur was shorter, its oscillations following the second sound after an appreciable period of quiescence (about 0.05 second) in the base line.

On May 26, 1935, after one month's freedom from attacks, a thorough examination of the patient was made. She felt quite well although she was still dyspneic on slight exertion. The facies was of the mitral type, with moderate acrocyanosis. Definite presystolic pulsations were visible in the cervical and brachial veins. Pulsations were detectable in the retinal veins, although accurate timing was not prac-

tiable. There was no inspiratory filling of the cervical veins. The liver edge was palpable 5.5 cm. below the right costal margin, and double pulsations were easily felt. There was no systolic thrill at the base; however, a forcible diastolic impact was plainly felt over the pulmonary orifice. No diastolic shock was palpable at the apex. The auscultatory findings were as previously described during sinus rhythm; the differentiation between the diastolic murmurs audible over the tricuspid and apical regions was still quite definite and was confirmed by several experienced examiners. The blood pressure was 120/80, and the vital capacity 2,500 c.c.

SUMMARY

The clinical diagnosis of acquired tricuspid stenosis is discussed. The various clinical manifestations attributable to the pathological physi-

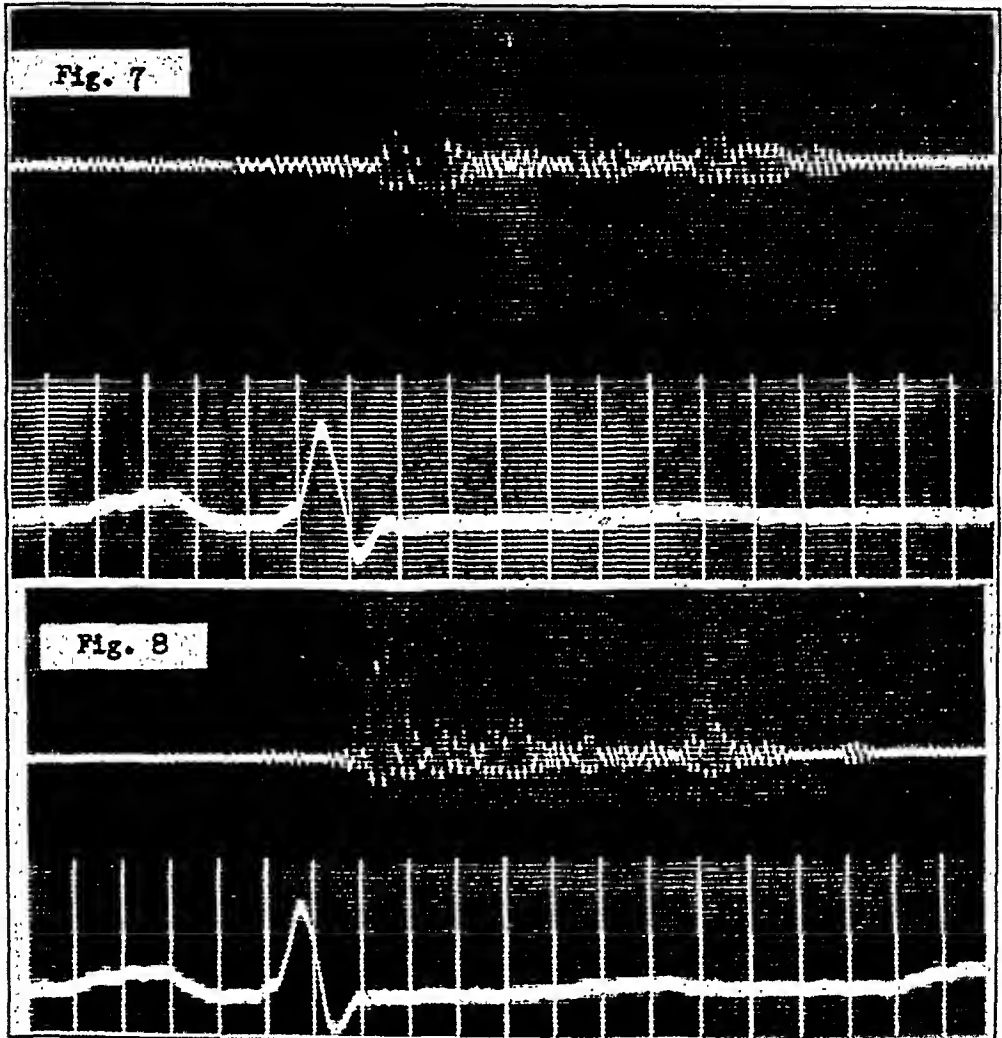


Fig. 7.—Simultaneous electrocardiogram and electrophonocardiogram* obtained with the microphone at the apical region, taken May 22, 1935. Time marker indicates $\frac{1}{25}$ (0.04) second.

Fig. 8.—Simultaneous electrocardiogram and electrophonocardiogram obtained with the microphone over the lower end of the sternum (tricuspid region); taken May 22, 1935. Time marker indicates $\frac{1}{25}$ (0.04) second.

*The electrophonocardiograms were obtained with the Western Electric Stethophone 1A and a Mathews Oscillograph, using a 130 high-pass filter, which permitted amplification and recording of all sounds above a frequency of 130 cycles per second. The tracings were taken by Dr. Wm. J. Kerr, Dr. J. B. Lagen, Dr. J. J. Sampson, and Dr. F. Keliogg.

ology of this condition are enumerated. A detailed case report is presented describing the course of a patient in whom all of the clinical findings typical of tricuspid stenosis were demonstrated during life.

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Department of Clinical Reports

NONPENETRATING WOUND OF HEART

RUPTURE OF PAPILLARY MUSCLE AND CONTUSION OF HEART RESULTING FROM EXTERNAL VIOLENCE: CASE REPORT*

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THE most common serious injury sustained by the heart is of the penetrating type produced by stab or bullet wounds. Case reports of these abound in the literature. Less common are those cases in which injury to the heart results from direct or indirect contusive forces without actual penetration of the myocardium.† Bright and Beek¹ have recently made a clinical and experimental study of nonpenetrating wounds of the heart in which they collected a surprisingly large number of instances from the literature (175 cases) in most of which (152 cases) the patient died of rupture of the heart. Of the remaining number, twelve patients survived the trauma, the diagnosis being made on clinical manifestations, and eleven patients died of myocardial failure at varying intervals after the trauma.

We are reporting here an additional case in which violence to the thorax caused rupture of a papillary muscle and contusion of the anterior surface of the left ventricle in a healthy young man who died from multiple complications twenty-six hours after the accident.

CASE REPORT

S. S., a seaman, aged twenty-four years, who had been in good health up to the time of his injury, was admitted to a general hospital near Boston in the morning at 6:50 following an automobile accident. At 4:30 A.M. on this same date, while asleep and riding in an automobile driven by a shipmate, an accident occurred; he was thrown violently from the car, and a truck ran over his upper abdomen. He was taken immediately to the Haymarket Square Relief Station, Boston, complaining of pain in the left kidney region posteriorly radiating into the flank. There a diagnosis was made of contusion of the abdomen with possible rupture of the spleen or left kidney. He was given first aid treatment for shock and directly transferred by ambulance to the general hospital.

On admission to the hospital ward he was conscious but apparently suffering from hemorrhage and shock. The skin was cold and pale; the pulse was rapid and weak; and he was still complaining of severe pain in the left kidney region posteriorly and of a severe headache.

On examination he was noted to be well developed and well nourished. There were minor lacerations above the left ear and small contusions in the parietal and oc-

*From the Cardiac Laboratory of the Massachusetts General Hospital.

†Among 7,600 autopsies at the Massachusetts General Hospital, where there is a busy accident service, it happens that there is not a single case of cardiac trauma of any type on record.

capital regions of the scalp on the left. The pupils were contracted, due to morphine, but reacted equally to light both directly and contralaterally. There was no nystagmus or evidence of hemorrhage from the nose or ears. The mucous membranes were pale. Movements of the neck and tongue were normal. The nasopharynx and throat were normal. The chest expansion was apparently equal on the two sides but limited bilaterally by pain in the left kidney region. Anteriorly there were no abnormal signs over the lungs. The chest was not examined posteriorly. There was no apparent cardiac enlargement. The heart action was regular at a rate of 88; the sounds were of good quality; and there were no murmurs. The blood pressure was 100 mm. systolic and 70 mm. diastolic. The entire abdomen was tense. There were a boardlike rigidity and tenderness in the left upper quadrant though he did not complain of much pain there. There were lacerations on the left wrist, in the right scapular region, and on the posterior aspect of the left thigh.

He vomited once, the vomitus being free of blood. The usual measures to combat shock were instituted with fairly good response.

Portable x-ray films of the abdomen and chest were reported as showing a fracture in the midportion of the eleventh rib on the left. The lower one-half of the left kidney shadow was visible, the upper portion being obscured by gas. The diaphragm and the heart were in their usual normal positions. The lung fields were slightly blurred due to motion, but there was no evidence of lung collapse or extensive pathological change within the chest.

Laboratory data were as follows: Urine—port wine in color, acid in reaction, specific gravity 1.026, albumin positive, sugar negative, sediment showing numerous red and white blood cells and a few finely granular casts. Hemoglobin, 60 per cent (Tallqvist); red blood cell count, 2,740,000; white blood cell count, 21,000 with 84 per cent polymorphonuclears; 16 per cent lymphocytes.

He was given a transfusion of 500 c.c. of whole blood following which an exploratory laparotomy under gas-ether anesthesia disclosed a ruptured spleen with free blood in the peritoneal cavity. The spleen was removed.

His condition was never satisfactory following the operation. He developed cyanosis of the lips and extremities; the pulse became more weak and rapid; and the heart sounds became poor in quality, approaching each other in intensity. The lungs showed signs of advancing pneumonia and the breathing became increasingly more labored, with loud bronchial sounds. The blood pressure, as recorded several hours following the operation, was 112 mm. systolic and 50 mm. diastolic. In spite of intravenous injections of fluid and digitalis, and the administration of oxygen he grew steadily worse, his temperature rose to 107.4° F., and he died about twenty-six hours following his injury.

Post-mortem examination revealed a well-developed white adult male, aged twenty-four years. There were small lacerated wounds over the posterior aspect of the right shoulder and over the right iliac crest. There were a slight abrasion on the left thigh and a superficial laceration of the scalp just above the left ear.

Peritoneal Cavity.—On opening the peritoneal cavity a moderate amount of old free blood was found. The stomach and transverse colon were dilated and there was subserous hemorrhage in the fundus of the stomach and in the descending colon at the splenic flexure. There was hemorrhage into the gastrocolic omentum and within the leaves of the mesentery of the descending colon. The superior mesenteric vessels showed marked congestion with hemorrhagic infiltration about them. The great veins of the abdomen were markedly dilated. *Appendix and esophagus* were normal. *Mesenteric and retroperitoneal glands* were normal. *The liver* was normal. An extensive hemorrhage was present in the left leaf of the diaphragm.

Pleural Cavities and Lungs.—The lungs were free in the pleural cavities except for a few easily broken adhesions over the left base posteriorly. The right lung

weighed 1,200 gm. It was quite edematous and in the upper lobe there was an area of increased consistency, which, on cut section, showed an early stage of red hepatization. The left lung weighed 1,300 gm. and at the junction of the upper and lower lobes laterally showed an irregular hemorrhagic contusion about 4 cm. in diameter. The lower lobe was of increased consistency in its lower two-thirds. The upper lobe showed increased consistency only under the hemorrhagic area where cut sections revealed patchy bronchopneumonia of a later stage than in the lower lobe. The eleventh rib on the left was fractured transversely in the posterior axillary line producing a hematoma beneath the pleura. *Bronchial glands* were normal. *Thyroid and parathyroid glands* were not examined.

Pericardium.—The pericardial sac contained about 200 c.c. of serosanguineous fluid; there was no pericarditis.



Fig. 1.—Photograph showing ruptured papillary muscle. The arrow points to the area in the myocardium from which the papillary muscle has been torn away at its base. Opposite this area on the external surface of the left ventricle is a purplish contusion.

Heart weighed 425 gm. The right ventricular wall measured 4 mm. in thickness, the left 15 mm. The cavities were not enlarged. The valves were essentially normal and measured in circumference as follows: mitral 9 cm., aortic 6.5 cm., tricuspid 12 cm., pulmonary 8 cm. In the left ventricle the anterior papillary muscle was ruptured at its base producing a hemorrhagic lesion 2 by 2.5 cm. wide by 1 cm. deep within the myocardium. Overlying this area on the external surface of the left ventricle there was a purplish spot 3 by 1.5 cm. in area. This was in the region of a small descending branch of the left circumflex artery of the heart, but there was no thrombosis or extensive rupture of the coronary arteries.

Coronary Arteries and Aorta.—The coronary arteries were patent, and the aorta was normal. *Pulmonary arteries and venae cavae* were normal.

Gallbladder and bile ducts were normal. *Pancreas and ducts* were normal.

Spleen.—The pedicle of the spleen remained. An accessory spleen was present with slight laceration of the capsule of the upper pole.

Kidneys.—Only the left kidney was examined. Its weight was 200 gm.; the consistency was normal; the capsule stripped with ease; medulla and cortex were of normal thickness; and passive congestion was present throughout. The perirenal tissues about the left kidney, including the *adrenal gland* showed hemorrhagic infiltration. *Pelvis, ureters, and prostate* were normal.

Urinary Bladder.—Greatly dilated, containing about 500 c.c. of dark amber-colored urine. No evidence of trauma to the bladder.

Anatomical Diagnoses.—Fracture, simple, left eleventh rib, posterior axillary line. Ruptured papillary muscle, left ventricle. Contusion of heart, left ventricle. Pleuritis, hemorrhagic, left. Bronchopneumonia, bilateral. Postoperative splenic pedicle in good condition. Supernumerary spleen with superficial laceration of capsule.

DISCUSSION

The extensive myocardial trauma in this case was but one of several serious injuries, and yet the efficiency of the damaged heart muscle allowed survival for more than twenty-four hours after the accident. It is impossible to say what might have been the result in the absence of the noncardiac complications; certainly the chances for repair of the injured heart muscle would have been greater, possibly even to the point of complete recovery. Old unexplained myocardial scars discovered post mortem may perhaps at times be the end-result of cardiac trauma of this type not recognized clinically. Had the tear in this case been a little deeper, however, the left ventricular wall would have ruptured through, producing sudden death from hemopericardium directly after the accident.

The numerous complications make this case of limited value in contributing to the clinical picture of contusive injury to the heart; it is of some significance, however, that cardiac trauma was not even suspected. The accident which was responsible for the cardiac injury also caused injury to the pleura, the lung, and the diaphragm. This resulted in rapidly advancing pneumonia which the patient was unable to combat, because of loss of blood and the shock.

Electrocardiography would have been invaluable in establishing a cardiac diagnosis ante mortem in this patient. We believe that this procedure should be carried out, where possible, in all cases of violent injury to the chest.

SUMMARY

A case of nonpenetrating wound of the heart muscle with rupture of a papillary muscle and contusion of the left ventricular wall from external violence is reported. Death resulted twenty-six hours after the injury, from loss of blood, shock, and an overwhelming pneumonic infection following the removal of a ruptured spleen. There were no significant clinical findings suggesting cardiac trauma.

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A CASE OF ANEURYSM OF THE PULMONARY ARTERY*

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ANEURYSM of the pulmonary artery is a relatively rare condition but one which occurs with sufficient frequency that it must be considered in the differential diagnosis of mediastinal tumors. Wahl and Gard¹ in 1931 were able to collect only seventy proved cases, and Scott² in 1934 found ninety cases recorded in the literature. Among 915 cases of aneurysm, Crisps³ found four which involved the pulmonary artery, and Costa⁴ found only one such case in 20,000 autopsies. Additional cases have been reported by several authors,⁵ not all of which, however, were proved by necropsy.

Syphilitic aortitis is frequently an etiological agent although it is less prominent in pulmonary than in aortic aneurysms. Peek,⁶ in an extensive review of syphilis of the pulmonary artery, found only twelve absolutely proved cases. He states that the main trunk is involved almost exclusively and that the gummatous type of lesion is more common than the productive form, the reverse of that found in the systemic aorta. Atheromatous changes in the smaller branches of the pulmonary artery may increase the pressure in that circuit so that a dilatation of a similarly involved large vessel may occur. Karsner⁷ believes that arteriosclerotic changes are more frequently the cause of aneurysm of the pulmonary artery than of the systemic aorta. Other etiological factors include congenital malformations of the heart which throw unusual strain on the pulmonary aorta, endocarditis, trauma, pneumothorax, and congenital defects of the pulmonary vessels. The age incidence of aneurysm of the pulmonary artery is considerably lower than that of aortic aneurysm, since 40 per cent of the patients are under thirty years of age, whereas only 18 per cent of aortic aneurysms occur before this age.¹ The infrequency of aneurysm of the pulmonary artery may be accounted for by the lower pressure and lesser strain on the vessel walls within this circuit, and also by the lower incidence of syphilitic involvement of the pulmonary vessels.

CASE REPORT

D. F., a white male aged fifty-nine years, was admitted to the University Hospital because of a sharp pain which appeared first in the left shoulder and later in the axillary region. The pain in the shoulder radiated to the left elbow and was aggravated by motion. That in the axillary region was not influenced by motion or respiration but was worse at night and was rarely present during the day. On several occasions the left hand and forearm became cold and white, with intensification of the shoulder pain. There had been no edema, shortness of breath, anginoid

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pain, or other evidences of cardiac disease. The patient had had gonorrhea fourteen years before, but no history of a syphilitic infection was obtained.

The left upper thorax was more prominent than the right and the expansion of this area was slightly restricted. The right cardiac border was beneath the sternum and the left border of dullness in the fifth interspace was just outside the mid-clavicular line. There was a visible impulse in the second and third intercostal spaces and on palpation over this area a systolic impulse, a diastolic impact, and a rough systolic thrill were felt. Dullness extended 8 cm. to the left of the mid-sternal line in the second interspace, 10 cm. in the third, and 8 cm. in the fourth. Auscultation over the area of abnormal pulsation revealed a very loud, rough systolic murmur ending in an accentuated and tympanitic second sound. The murmur was transmitted to the entire left upper thorax but not to the vessels of the neck. The aortic second sound was normal and only a faint systolic murmur was heard, which was not transmitted upward. A soft systolic murmur was also heard at the apex. There were no diastolic murmurs, and the cardiac mechanism was normal. The blood pressure was 132/78 in the right, and 134/84 in the left arm. The pulsa-

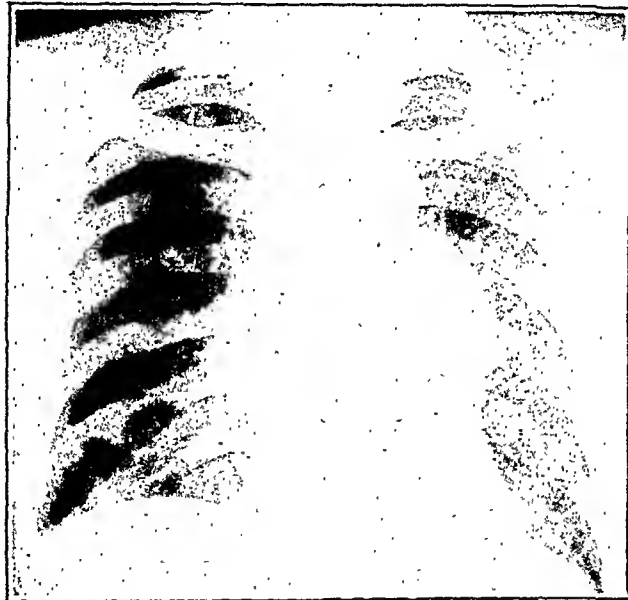


Fig. 1.

tion in all accessible peripheral arteries was normal and symmetrical. There was no tracheal tug and no pulsation in the suprasternal notch. A slight degree of cyanosis was noted on the lips and finger tips. The pupils were irregular but responded to light and in accommodation. The nasal septum was intact, and the reflexes and sensations were normal. Motion of the left shoulder was limited by pain, but there was no crepitation, muscle atrophy, or other objective evidence of joint involvement. The Wassermann reaction was strongly positive. Fluoroscopic examination showed a well-outlined, rounded shadow in the region of the pulmonic curve on the left. This had a definite expansile pulsation. In the oblique and lateral views this shadow was separated from the heart and from the thoracic aorta. Right posterior oblique and left lateral roentgenograms showed a tumor in the left hilum area extending laterally but not posteriorly. The thoracic aorta was uninvolved. A roentgen-kymogram showed a pulsating tumor mass. The patient received ten intraosseous injections of bismuth and was discharged from the hospital. He returned six months later, having taken potassium iodide gr. xv daily during the interval. The pain in the shoulder and elbow had entirely disappeared, and he experienced only a throbbing sensation in the left upper chest. He was feeling much

better and was able to do light work, although there was no change in the physical or roentgenological findings. The patient returned to his home and continued to do light work without discomfort. Five months later, however, he died very suddenly from what was interpreted by his physician as a ruptured aneurysm.

The physical signs of aneurysm of the pulmonary artery as given by Henschen⁸ are as follows:

1. Prominence, dullness and an x-ray shadow in the second and third left intercostal spaces.
2. Pulsation and thrill in the same area.
3. A loud, superficial, rasping systolic murmur.
4. Absence of signs of aortic aneurysm.
5. Absence of dilatation of the left heart.
6. Right-sided cardiac hypertrophy.
7. Intense cyanosis, congestion, hemoptysis and substernal pain.

If the aneurysm is uncomplicated by other valvular or vascular changes, there is no reason to suspect right ventricular hypertrophy; and since the cyanosis and congestion depend on pressure phenomena or cardiac insufficiency, they are not necessarily present. This case presents the essential diagnostic features, and, although terminating fatally, the subjective improvement for a period of a year after antisyphilitic therapy was very striking.

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Department of Reviews and Abstracts

Selected Abstracts

Hall, G. E., Ettinger, G. H., and Banting, F. G.: An Experimental Production of Coronary Thrombosis and Myocardial Failure. *Canad. M. A. J.* 34: 9, 1936.

Clinical degradation with severe myocardial and coronary artery damage was produced (in dogs) by the repeated injections of 1 to 10,000 injections of acetyl choline iodide or acetyl choline bromide. The damage was found in those areas most richly supplied with vagal postganglionic fibers. Clinical evidence of progressive myocardial failure with subsequent death was noted in every animal, and pathological examination showed permanent damage to the heart in all but two animals.

In those animals which at autopsy showed permanent damage to the heart, there was in the coronary arteries a hyaline degradation of the tunica media and a tendency to thrombosis. In the myocardium there was probably hyaline degradation or infection followed by extensive degradation with a fibrotic response.

AUTHOR.

Gregg, Donald E.: The Phasic and Minute Coronary Flow During Acute Experimental Hypertension, *Am. J. Physiol.* 114: 609, 1936.

The results presented elucidate the causes of the augmentation of coronary blood flow when the aortic pressure is elevated by increasing the peripheral resistance either mechanically or chemically. The essential factors which affect the distribution of flow between systole and diastole per beat are the relative magnitude, contour, time relations, and duration of the systolic and diastolic phases of the aortic and P.C.P. curves. The sum of the pressure differences involving all these factors gives an index of the flow per beat, and the product of cyclic flow and heart rate gives an index of the minute flow.

When all these effects are integrated during hypertension, the picture becomes somewhat complicated. Tentatively our concept is that as the aorta is compressed and the blood pressure and pulse pressure rise, the heart rate slows; the coronary systolic resistance decreases relative to the aortic systolic, thus permitting an actually greater inflow per beat during ventricular contraction, although the systolic resistance decreases relative to the aortic systolic, thus permitting an actually greater inflow per beat during ventricular contraction, although the systolic flow relative to diastolic is decreased. However, the minute systolic flow increases only moderately since, as the heart rate slows, the time occupied by systole is materially reduced. During diastole at the high pressures the diastolic interval lengthens, and the diastolic coronary pressure increases only slightly (a resultant of the slower heart rate tending to decrease it and the higher blood pressure tending to raise it) with the net result that the diastolic flow per cycle and per minute is tremendously augmented. Quantitatively, although the flow in both phases of the cardiac cycle is greater, the augmentation of flow is chiefly diastolic.

When the hypertension is produced by epinephrine the same alterations of flow occur, except that the coronary systolic resistance may approximate aortic systolic, if the latter is not too high, with the result that systolic flow per beat and per minute is reduced to a small value.

Finally, the conclusion is reached that the dominant factor increasing the myocardial blood supply in acute experimental hypertension is a combination of mechanical changes of which the most important is the aortic head of pressure throughout the cycle, together with the relative increase in the time per minute occupied by diastole. Aiding this are additional mechanisms: the relative decrease of systolic coronary resistance at high aortic pressures and pulse pressures, the slightly decreased coronary diastolic resistance at the slower heart rates, and finally, slight changes in the form of the P.C.P. curve.

AUTHOR.

Mayne, Walter, and Katz, Louis N.: Observations on the Path Taken by the Pain Fibers From the Heart, *Am. J. Physiol.* 114: 688, 1936.

Evidence is presented to show that cardiac pain fibers traverse the nerve plexus located in the posterior mediastinum which connects the deep cardiac plexus with the thoracic sympathetic chain from the sixth up to the first thoracic segment and possibly also with the cervical sympathetic chain.

Severance of the fibers in the posterior mediastinum was found to abolish the affective response obtained on stimulating the nerve plexus surrounding the coronary blood vessels.

The feasibility and possible physiological advantages of this operation in patients with angina pectoris are discussed.

AUTHOR.

Maltby, Alice B., and Williams, John E.: Attempts to Apply the Acetylene Method of Determining the Cardiac Output to the Dog, *J. Lab. & Clin. Med.* 21: 354, 1936.

Simultaneous blood and alveolar samples taken from the dog at various intervals after the beginning of forced rebreathing of an air-acetylene mixture show that a requisite equilibrium between the acetylene tension in the alveolar air and in the blood can be attained. As a rule, such equilibrium was not established before fifteen seconds of rebreathing at the approximate rate of a complete respiration every two seconds. This fact is not favorable to the acetylene method since a second requisite for its validity is the securing of at least two adequately spaced samples before the completion of one circulation and since investigations have been reported (Starr and Collins) indicating return of blood to the heart in such a short period (fifteen seconds) that obviously it would be impossible to obtain two samples within such a period if the first sample is not secured before the fifteenth second.

A comparison of the values obtained for the cardiac output of five dogs by the acetylene method with the values obtained by the direct Fick method shows that the results obtained by the acetylene method are nearly 32 per cent too low in one case and about 50 per cent too low in each of the other four cases.

Tests on the same dog by the acetylene method give wide variation in results, which would preclude its use for comparison of output values before and after production of a circulatory disturbance.

Comparison of the average cardiac index calculated from the acetylene tests (2.15) with the average found in a series of normal dogs by the Fick method (3.95) indicates that the index by the acetylene method is much too low (average 46 per cent).

AUTHOR.

Yater, Wallace M., Cornell, Virgil H., and Claytor, Thomas: Auriculoventricular Heart-Block Due to Bilateral Bundle-Branch Lesions: Review of the Literature and Report of Three Cases With Detailed Histopathological Studies, *Arch. Int. Med.* 57: 132, 1936.

Three cases of auriculoventricular heart-block due to lesions confined to both bundle branches are reported with detailed histopathological studies. The pathogenesis was probably coronary arterial disease in all.

Such lesions of the bundle branches are probably a common, if not the commonest, cause of auriculoventricular heart-block.

The heart may appear grossly normal, with or without gross evidence of coronary arterial disease. The morbid anatomy is usually that of a fibrous replacement which does not necessarily completely destroy the continuity of the bundle branches. Microscopically as well as grossly, the myocardium may appear normal or relatively little affected. This fact indicates that the conduction system is more susceptible to diminution of blood supply than the myocardium is, since there is a common blood supply. If the patient lived longer, similar changes might develop in the myocardium.

The freedom of the auriculoventricular node and bundle from similar lesions in such cases is due to the fact that their blood supply comes from a source different from that of the blood supply of the bundle branches and from a portion of the coronary arterial tree less often and less severely affected by degenerative changes.

Lesions confined entirely to one bundle branch are apparently rare because of the common source of the blood supply of the right bundle branch and the anterior division of the left bundle branch from the anterior descending artery, which is most often and most seriously affected by degeneration.

The form of the ventricular complexes is frequently suggestive of bundle-branch block, and variation in the form of these complexes is common. These variations suggest a shift in the site of the pacemaker, sometimes from one side of the septum to the other. The ventricular complexes may be of supraventricular form, however; and then there are either two pacemakers, one in each bundle branch, generating impulses simultaneously or, more probably, a single pacemaker in one or the other branch sending impulses directly through the interventricular septum into the Purkinje network of the contralateral ventricle as well as into that of the homolateral ventricle.

There may be a variability from time to time in the degree of auriculoventricular dissociation, indicating that there are other factors involved besides the organic lesions of the bundle branches.

In such cases as these, death frequently occurs in an Adams-Stokes attack.

More frequent and more careful histopathological studies of the entire recognizable conduction system are urgently needed because of the uncertainties at present involved in the interpretation of electrocardiographic alterations.

AUTHOR.

White, Paul D.: Coronary Disease and Coronary Thrombosis in Youth. *J. M. Soc. New Jersey* 32: 596, 1935.

Observations on two groups of patients with coronary thrombosis under the age of forty years are recorded. One group included fourteen cases, the other seven. All were males. The case histories showed very few infections. The family histories were good or excellent in six of the first group. Hypertension was present in none. Angina pectoris followed the coronary thrombosis in five cases. Only three of the patients have died. The findings in this group afford

certain clues which may prove helpful in the analysis of cases and in prevention. The male sex is overwhelmingly the victim in early life. This presents the outstanding clue. The young men all used considerable amounts of tobacco.

It is also to be noted that the men lived city lives and did not exercise consistently. Infections do not seem to play much of a rôle in the induction of certain coronary diseases nor does diet, although further study may show that, as in diabetes, a combination of faulty metabolism plus faulty diet is important.

H. McC.

Elliot, Albert H., and Evans, Richard: Clinical and Electrocardiographic Picture of Coronary Occlusion Produced by Ruptured Aneurysm of the Abdominal Aorta, *Am. J. M. Sc.* 191: 196, 1936.

An instance is reported of ruptured aneurysm of the abdominal part of the aorta in which, because of coma, the subjective symptomatology could not be obtained. The clinical picture strongly suggested shock following coronary occlusion. Electrocardiographic changes, which were characteristic of and before death were diagnosed as those of coronary occlusion, are seen in retrospect to have been probably due to a relative ischemia of the myocardium without infarction. This ischemia depended on thickened coronary arteries and the reduced circulating blood volume following hemorrhage.

AUTHOR.

Edeiken, Joseph, and Wolferth, Charles C.: Persistent Pain in the Shoulder Region Following Myocardial Infarction, *Am. J. M. Sc.* 191: 201, 1936.

Fourteen cases with persistent pain in the shoulder region following myocardial infarction have been briefly described. It is suggested that the incidence of this symptom among survivors from infarction may exceed 10 per cent.

The pain may be mild or severe and was usually described as burning, aching, or wrenching. The left shoulder is usually involved although the right may also be affected. The pain may shift from one shoulder to the other. Occasionally the pain may be greatest in the region of the biceps or deltoid muscles.

It may begin coincidentally with an attack of coronary occlusion up to at least sixteen weeks after the attack.

The pain persisted from seven weeks to over five years.

Local treatment to the shoulder has proved ineffective. Deep roentgen ray therapy has been tried in several cases without consistent results.

Most patients in this group had foci of infection. A few had slight cervical or upper dorsal spondylitis. Nevertheless, the frequency of occurrence after myocardial infarction and the time relations to the attacks, suggest that the cardiac lesion is an important etiological factor. An analogy to causalgia is suggested.

AUTHOR.

Donovan, H. C. E.: Heart Disease Complicating Pregnancy, *Brit. M. J.* 2: 104, 1936.

Most patients with heart disease are capable of passing successfully through pregnancy; it is the labour which tests the heart's efficiency.

Therapeutic abortion is indicated principally in cases of cardiac reinfection during pregnancy, the few patients who are getting worse in spite of bed and digitalis treatment and those with the more severe forms of aortic disease and congenital malformation.

In deciding for or against Caesarean section the general and obstetric history and the capacity for household work are the main points on which the decision turns.

A surgically induced labour may be, and usually is, more trying than normal labour. The risks are less easily calculated than are those of Caesarean section, and it is rarely good treatment after three months' gestation.

The purely operative risks of Caesarean section have been so much reduced by the lower uterine segment operation and the newer antiseptics, especially dettol, that one operates nowadays with far more confidence.

AUTHOR.

Hoyne, Archibald L.: Causes of Death in Diphtheria and Their Prevention. *Am. J. M. Sc.* 191: 271, 1936.

When the diphtheria membrane is located within or below the larynx, diphtheria antitoxin alone will seldom save the patient. Usually intubation or tracheotomy is required.

Although there is no absolute method for preventing bronchopneumonia in diphtheria, the frequency of this complication can be held to a minimum if minute attention is paid to cleanliness of hands and instruments when performing intubations and if correct methods of feeding are followed for patients wearing intubation tubes.

Diphtheritic myocarditis can often be prevented by the use of 10 per cent dextrose solution intravenously, provided this treatment is begun sufficiently early and continued daily for a sufficient length of time.

Dextrose helps to maintain the general nutrition of the patient who may be unable to swallow or retain food. In addition, it seems to provide nourishment to the heart muscle and thus lessen passive congestion of the liver. The necessity for immediate institution of glucose therapy increases according to the number of elapsed days prior to antitoxin injection.

AUTHOR.

Fischer, Robert, and Wasserbrenner, Klemens: Paroxysmal Ventricular Tachycardia in Calcification of the Pericardium, *Med. Klin.* 31: 1171, 1935.

The authors suggest that the paroxysmal tachycardia in the thirty-five-year-old patient reported was due to calcification of the pericardium. This calcification was identified by x-ray and was the only abnormality found on clinical examination. Quinidine prevented the recurrence of the attacks.

L. N. K.

Winkelbauer, A., and Schur, M.: On Surgical Therapy of Adhesive Pericarditis. *Med. Klin.* 31: 1231, 1935.

The authors report and discuss in detail eight cases of adhesive pericarditis in which surgical intervention was employed. They conclude that when ascites is prominent, an attempt should be made to free the mouth of the inferior vena cava from adhesions and when hydrothorax is prominent, the surgeon should concentrate on freeing the adhesions encumbering the left ventricle. The decoration of the anterior wall of the right ventricle should be deferred until after the heart is freed from the diaphragm and the posterior chest wall. There is no reason why the operation cannot be done in several stages. The condition of the heart is the factor determining how many stages the operation should require. The electrocardiogram and the amount of peripheral edema are especially valuable in estimating the cardiac state. In severely damaged hearts a

single-stage operation is hazardous. In hearts with advanced involvement it is best to do only a Brauer cardiomyolysis. When the patient's condition permits, the surgeon can start severing the adhesions, preferably over the left margin of the left ventricle. Further decortication can then be done at later stages. It is best to stop the operation whenever the pulse and blood pressure indicate weakening of the cardiac power, even with an apparently healthy myocardium. Great care must be used when calcified plaques are encountered. When these plaques are on the epicardium or when the epicardium and parietal pericardium are closely adherent, it is best to avoid the region containing the plaque since irreparable tears of the myocardium can easily be produced. The authors prefer to make a large flap over the left lateral chest wall rather than to use the anterior transpleural incision. The lateral approach not only has the advantage of the cardiomyolysis operation, but also permits better access for decortication of the posterior and inferior surfaces of the heart.

L. N. K.

Meyer, Otto: On the Problem of "Growing-Pains," München. med. Wehnsehr. 82: 1523, 1935.

The author claims that in most patients with "growing-pains" seen by him he could demonstrate a latent phlebitis in the legs, both by pressure over the veins (by a special technic which he describes) and by other considerations previously reported by him. The cardiac complications are ascribed to bacterial toxins produced in the infected veins.

L. N. K.

Werner, Sidney C.: Rheumatic Cardiac Disease: Association of Active Rheumatic Fever With Heart Failure, Arch. Int. Med. 57: 94, 1936.

A study has been made of 100 consecutive cases of rheumatic cardiac disease with heart failure in wards, of 75 cases of the same condition with autopsy, and of 50 cases of syphilitic cardiac disease included for comparative purposes.

Signs of active rheumatic fever have been demonstrated in 45 per cent of the clinical cases of rheumatic cardiac disease. Activity has been suspected in an additional 21 per cent.

In the pathological material, active lesions have been found in 66 per cent of the cases of rheumatic cardiac disease.

An exertional or mechanical factor associated with cardiac insufficiency was definite in only 8 per cent of the cases of rheumatic cardiac disease and 7 per cent of the cases of syphilitic cardiac disease. There was no demonstrable factor in the remaining 26 per cent and 48 per cent of the cases of rheumatic and syphilitic cardiac disease, respectively.

Infection of the respiratory tract is concomitant with the loss of cardiac reserve in 50 per cent of the clinical cases of rheumatic and syphilitic cardiac disease.

A seasonal rise in the number of patients with rheumatic fever admitted to the hospital for cardiac insufficiency is indicated, corresponding to the known statistics on morbidity for rheumatic fever in New York City. The finding is not demonstrable in the series with syphilitic cardiac disease.

AUTHOR.

Yater, W. M., and Leffler, H. H.: Massive Lymphosarcomatous Invasion of the Heart (Report of a Case). M. Ann. District of Columbia 4: 253, 1935.

Metastases to the heart are uncommon, but they have occurred from neoplasms of all the main organs. Carcinomatous metastases are more common than sarcomatous. The invasion of the heart apparently occurs by way of the blood

stream. Serious cardiac dysfunction rarely results, and in the case reported there was nothing to indicate any injury to the heart muscle. Occasionally congestive heart failure occurs; sudden death has occurred; subacute bacterial endocarditis may be simulated; and heart-block is rarely caused by tumor. Of great value in the diagnosis of metastatic invasion of the heart is the onset of auricular fibrillation or auricular flutter in a case of recognized malignant neoplasm of some other organ. Bloody fluid in the pericardial sac is also suggestive, and a localized enlargement or an irregularity in the outline of the heart in the roentgenogram should bring the possibility of tumor of the heart to mind.

The case presented is that of a forty-nine-year-old colored woman who suffered a fatal illness with symptoms of about ten weeks' duration. Although it was evident that she was suffering from some malignant neoplastic disease, the exact diagnosis was undetermined during life. At no time were there symptoms or signs of cardiac disease. At necropsy it was found that a lymph node behind the head of the pancreas had taken on malignant properties, invaded the pancreas, and then disseminated its cells through the blood stream to the liver, kidneys, spleen, heart, and lungs. The metastatic lesions far surpassed the primary lesion in size, and the heart showed great invasion of the walls of both chambers by tumor. Nodules projected outward beneath the epicardium and inward beneath the endocardium. Microscopic study showed typical lymphosarcoma.

AUTHOR.

Shelburne, Samuel A.: Primary Tumors of the Heart; With Special Reference to Certain Features Which Led to a Logical and Correct Diagnosis Before Death, *Ann. Int. Med.* 9: 340, 1935.

This report, the second in medical literature, describes the signs, symptoms, and histologic appearance of a primary tumor of the heart which was correctly diagnosed before death. According to Gottel (1919), the first clinical diagnosis of this condition was made by Pavlowsky. The differential diagnosis which led to the correct assumption in this instance was also found applicable in two others found among autopsy records; it should lead more frequently to the correct diagnosis, whenever an otherwise unexplainable bloody pericardial effusion is encountered. Other signs and symptoms have not infrequently led to a diagnosis of secondary tumor but are unreliable in the diagnosis of primary tumors.

AUTHOR.

Prinzmetal, Myron, and Wilson, Clifford: The Nature of the Peripheral Resistance in Arterial Hypertension With Special Reference to the Vasomotor System. *J. Clin. Investigation* 15: 63, 1936.

Determinations of resting blood flow in the arm in various types of hypertension (benign, malignant, and secondary) give an average value no greater than that obtained from subjects with normal blood pressure. This indicates that increased vascular resistance in the different types of hypertension is not confined to the splanchnic area but is generalized throughout the systemic circulation.

Patients with hypertension show increase in blood flow in response to heat and reactive hyperemia equal in degree to that produced in normal individuals, showing that the blood vessels in hypertension are capable of considerable dilatation and indicating that the increased peripheral resistance is due to hypertonus and not to organic changes in the vessel walls.

Sympathetic vasodilatation produced by the "heat test" produces no greater increase in blood flow in subjects with high blood pressure than in normal individuals, suggesting that the vascular hypertonus is not vasomotor in origin.

Patients with coarctation of the aorta, on the other hand, show a greater increase in blood flow in the arm in response to the heat test than controls or patients with generalized hypertension. This demonstrates that vasoconstriction of sympathetic origin is present in the upper extremities in coarctation of the aorta, and affords confirmatory indirect evidence that the hypertonus in generalized hypertension is not of vasomotor origin. Sympathetic vasoconstriction in the upper extremities in coarctation of the aorta may be regarded as a compensatory mechanism which maintains the normal distribution of blood throughout the body.

Anesthetization with novocaine of the vasomotor nerves to the arm produces the same increase in flow in normal subjects and patients with hypertension, proving that the vascular hypertonus is independent of the vasomotor nerves, and that this hypertonus must therefore be regarded as intrinsic spasm of the blood vessels themselves.

Acute exacerbation of hypertension with change from the benign to the malignant type has been observed in one case. Such exacerbation is apparently not due to increased vasomotor activity but must be attributed to an increase in the intrinsic vascular hypertonus.

The above conclusions apply to all types of hypertension studied; namely, benign hypertension, malignant hypertension, and "renal" hypertension associated with acute and chronic glomerulonephritis and chronic pyelonephritis; hence there is no physiological evidence for the separation into "organic" and "functional" types or for the assumption that renal hypertension is due to vasomotor hypertonus.

It has been shown in both normal subjects and in patients with hypertension that there is vasoconstrictor and vasodilator innervation to the blood vessels of the arm. In this region greater variations in blood flow are produced by vasodilator than by vasoconstrictor impulses. In the types of hypertension studied, it appears therefore that normal vasomotor activity is superimposed on the intrinsic vascular hypertonus.

Surgical procedures aiming at the relief of high blood pressure by sympathectomy do not abolish the vascular hypertonus which is fundamentally responsible for the hypertension.

AUTHOR.

Thompson, Kenneth W., and Dunphy, John E.: Intraabdominal Apoplexy. *Ann. Surg.* 102: 1116, 1935.

Intraabdominal apoplexy is the spontaneous rupture of an arteriosclerotic artery of one of the abdominal viscera. The case presented appears to be the eighth reported in the medical literature. A woman sixty-two years old was awakened by severe pain in the left precordial and left upper abdominal regions seventeen hours before admission to the hospital. The pain gradually spread to the entire abdomen and soon was associated with nausea and attempts to vomit. Examination at the hospital showed abdominal distention and tenderness, shifting dullness in the flanks, and some involuntary muscle spasm. The blood pressure was 120 systolic and 70 diastolic. Abdominal exploration revealed a large amount of liquid blood and much clotted blood in the peritoneal cavity. The gastrohepatic omentum was a thickened hemorrhagic mass, apparently the site of the hemorrhage, although no bleeding point was found. The patient was well six months after operation.

E. A.

Kerr, H. H.: Aortic Embolectomy. *M. Ann. District of Columbia* 4: 249, 1935.

The author describes the symptoms and findings in a case of operative removal of a saddle embolus of the aorta. As a result of this study he suggests that in cases of saddle embolus the femoral artery be exposed in Scarpa's Triangle under local anesthesia. A soft rubber tube, slightly smaller than the lumen of the vessel and attached to a suction apparatus, should then be passed into the vessel a centimeter at a time after thorough lubrication with sterile oil. After advancing the tube up the vessel 1 cm. it should be withdrawn and again advanced up the vessel an additional centimeter. In this way, advancing the suction a centimeter at a time, any clot in the vessel may be caught in the tube and withdrawn. Should the tube be forced directly up to the bifurcation there would be danger of forcing the embolus into the opposite iliac system.

Such a surgical attack upon a saddle embolus of the aorta would be a minor procedure compared with the extensive abdominal dissection that is necessary to expose the aorta and its bifurcation. In case of embolic block of the main vessels of the upper extremity in the axilla, or of the lower extremity at the femoral or popliteal area, the same procedure could be carried out.

H. McC.

Ettinger, G. Harold, and Hall, G. Edward: Synergy of Adrenaline and Acetylcholine on the Pulmonary Blood Vessels in the Rabbit. *Quart. J. Exper. Physiol.* 25: 18, 1935.

The tunica media of the pulmonary artery and arteriole of the rabbit is capable of causing death by firm contraction. It has an abundant nerve supply apparently capable of handling wide variations in the contractile state of the artery, but the feeble reactions of the pulmonary artery to adrenalin and sympathetic stimulation indicate that the sympathetic nerves would hardly control the necessary variations in caliber. The powerful vasoconstricting effect of acetylcholine coupled with results of vagus stimulation suggests that the vagus or other parasympathetic fibers may be responsible for the greater part of the vasoconstriction.

E. A.

Kirklin, O. L.: Obstruction of the Right Innominate and Left Subclavian Arteries With Orthostatic Syncope. *Proc. Staff. Meet. Mayo Clinic* 10: 673, 1935.

A man fifty years old complained of attacks of syncope preceded by blurring of vision. On several occasions he had experienced sensations of fainting without losing consciousness. All the episodes occurred when the patient was in the erect posture. The blood pressure could not be determined in the right arm; in the left arm it was 70 systolic and 60 diastolic when the patient was recumbent; it was somewhat lower when the patient sat and could not be determined when he stood. Pulsations were absent in the right carotid, subclavian, axillary, brachial, radial, and ulnar arteries. Pulsations were faint in the left subclavian, axillary, brachial, radial, and ulnar arteries when the patient lay and disappeared when he stood. The nature of the lesion occluding the right innominate and subclavian arteries could not be determined. The brain received its blood from the left carotid artery alone and digital occlusion of it caused syncope. Ephedrine sulphate was used therapeutically but sufficient time had not elapsed to determine its efficiency.

E. A.

Roome, Norman W., and Wilson, Harwell: Experimental Shock. The Effects of Extracts From Traumatized Limbs on Blood Pressure. Arch. Surg. 31: 361, 1935.

Two theories suggested as the mechanism of traumatic shock have received most attention recently: (1) that of absorption of metabolic toxins from traumatized area which effect vasodilation and increased permeability of capillaries and (2) that of local loss of blood or plasma, or both, resulting in a serious decrease in the volume of circulating blood. Experiments on dogs are described in which extracts obtained from traumatized limbs were perfused in a second animal. Preliminary experiments showed that such extracts were markedly hemocoagulant, contained particles of fat and of tissues, and almost invariably caused death when injected intravenously. Extracts purified by centrifugation when injected into a heparinized animal caused a rise in blood pressure; if the bloody fluid was removed before centrifugation, the extract did not cause a sustained fall in blood pressure or death. The "toxic theory" was not supported by the experiments.

E. A.

Goldhammer, St., Leiner, G., and Scherf, D.: The Amount of Circulating Blood Before and After Mercury Diuresis. Klin. Wehnschr. 46: 1109, 1935.

Determination of the amount of circulating blood with CO and trypan red method in fourteen cases of heart failure showed a diminution in the amount of circulating blood twenty-four hours after salyrgan injections. The diminution paralleled the amount of diuresis and loss of weight. The plasma volume and red cell count were found to be diminished. The results are not due to reduced amount of blood but to diminished water retention in the tissues. There appears to be a shift of blood from the liver and large veins to the periphery.

J. K.

Starr, Isaac, Jr.: Acetyl- β -Methylcholin: IV. Further Studies of Its Action in Paroxysmal Tachycardia and in Certain Other Disturbances of Cardiac Rhythm, Am. J. M. Sc. 191: 210, 1936.

Acetyl- β -methylcholin has been used in the treatment of 75 attacks of paroxysmal tachycardia in 37 patients. In 66 instances (88 per cent) the attack was promptly brought to an end.

The dosage necessary to terminate attacks of paroxysmal tachycardia varies with the age as well as with the weight of the patient.

Quinidine antagonizes the cardiac action of acetyl- β -methylcholin and may well be responsible for the failure to bring attacks of paroxysmal tachycardia to an end in certain cases.

In auricular flutter change in the rhythm can occasionally be brought about by acetyl- β -methylcholin.

In one case the frequency of ventricular extrasystoles was diminished by the drug.

The effects of overdosage of the drug are described. The symptoms are closely analogous to those of the ordinary attack of syncope.

AUTHOR.

Book Review

DIGITALIS. By Dr. H. Weese, Leipzig, Georg Thieme, 1936, 296 pages.

This review of the literature is presented in eight chapters, differing widely in length and importance, with an extensive index, and with a table of contents which, with its many subdivisions, exceeds in length (7 pages) the space allotted to this review. There are more than 1,200 references to the literature, which is analyzed with skill.

The first chapter presents a brief review of the history of digitalis. After Withering had proved its extraordinary value in the treatment of cardiac disease, it was employed in so many conditions for which it is useless that it was threatened with eclipse; and more than a century passed before the rational therapy of digitalis was reestablished.

The second chapter (27 pages, exclusive of 185 references) discusses the identification and standardization of digitalis bodies and chemical and biological methods of studying them. Regret is expressed that while we have an international standard of activity available for the whole world, the therapy constitutes a veritable Tower of Babel. The avowed purpose of the book is to bring about the desired standard of therapy.

The third chapter (30 pages, 258 references) treats of many drugs of this group, most of them cursorily; of their active and their inert principles; galenical preparations; and the chemistry of the principles of hitherto unknown constitution. Digitalis, strophanthus, and squill and their constituents are the only ones of much interest to the internist except in connection with the unceasing efforts of manufacturers to introduce substitutes for digitalis.

The fourth chapter (40 pages, 143 references) embraces the more recent chemistry of the glucosides of this group. Great strides have been made in this field in which American investigators occupy a prominent place.

The author explains much of the confusion that exists with regard to many of the names of digitalis principles, and their relationships to each other. He distinguishes as "genuine digitalis glucosides" those which are obtained by a process which is supposed to avoid chemical change, from those now in common use, including digitoxin and true digitalin.

The fifth chapter (40 pages, 151 references) discusses the biochemistry of digitalis glucosides. Absorption is considered at length, but the subject requires care on the part of the reader to avoid misunderstanding. Every student of this problem knows that the absorption of these glucosides varies widely with the mode of administration, with different principles, and with different species. One observer found that the infusion of digitalis is only one-thirtieth as active after oral administration as it is after injection, in one species. That does not apply to man, however.

The behavior of these glucosides in the blood, their distribution in the body, their elimination, by decomposition and by excretion, are all discussed at length, but there is no subject which stands in greater need of further study. Little is known of the fate of these substances in the body, and that little is confined mainly to the cold-blooded species in which the behavior differs widely from that in man. Practically nothing is known of the excretion of digitalis in the urine of man, or of the seat of its decomposition.

Cumulation, formerly considered mysterious, but which is merely persistence of action, is discussed from the experimental and the theoretical standpoints. The author maintains that the cumulative action of digitoxin is a toxic effect. That is difficult to reconcile with the commonly accepted facts of digitalis therapy.

The sixth chapter (79 pages, 450 references), entitled "Special Pharmacology," has more than one hundred subdivisions. It takes up the chief factors concerned in the effects of digitalis on the circulation. These include: the action on the isolated heart; the action on the vessels; the minute-volume of the circulation; the action outside of the heart, and, finally, the action on the intact circulation.

The prevalent confusion regarding the vasoconstrictor action of digitalis is explained, and the author states that the mistaken belief that digitalis constricts the coronaries led to its combination with various drugs of the xanthine group, including caffeine and theobromine. He finds no evidence that digitalis constricts the coronary vessels in man, or that these arteries behave differently toward digitalis from the other blood vessels of the body.

Weese concludes that the diuresis induced by digitalis is due in part a direct action on the kidneys, though it is due mainly to the actions on the heart. He finds no evidence that digitalis acts on the vasomotor centers or on any other part of the central nervous system. He concludes that digitalis acts peripherally, but not on the stomach, to induce vomiting, the exact seat being undetermined. Nevertheless, he implies that the saponin is of importance when digitalis is administered orally. That view is so thoroughly discredited that few will accept it.

The seventh chapter merely presents a tabulation of the activity of many members of the group with different methods of administration to the frog, cat, dog, rabbit, and pigeon, as presented by various investigators.

The eighth chapter is concerned with the therapeutic use of digitalis and its substitutes. The author states that digitalis glucosides (including all digitalis bodies) are the only substances that simultaneously decrease the rate of the heart; inhibit conduction; promote cardiac contractility; and improve the coronary circulation, without increasing resistance by vasoconstriction and interference with the increased work of the heart. Thus all the actions on the heart coincide to increase the function of the injured heart—that is, to maintain the optimum minute-volume of the circulation.

The author concludes that digitalis is useless in vascular collapse in the absence of cardiac injury, in acute infections, and in surgical operations, but that it is often of value in chronic infections when the heart has suffered injury.

The latter part of this chapter is devoted to the question of dosage. The author had previously objected to the use of pills because the active principles must be first extracted by the gastrointestinal juices and then absorbed. The objection is not valid so far as properly made tablets are concerned, though extraction and absorption must occur, of course. Weese expresses astonishment that Lewis (translation, 1935) does not mention the therapeutic use of strophanthin by intravenous injection. That astonishment will not be shared by the greater number of American cardiologists. On the other hand, Weese does not mention the most comprehensive study that has been made of the use of digitalis in the treatment of pneumonia—that conducted at Bellevue Hospital several years ago. In fact this chapter contains no reference to any American paper of later date than 1926. That fact alone would justify the criticism that this chapter might have been omitted without serious loss. This chapter affords an illustration of an obvious fact, but one which is often forgotten. It is the office of the pharmacologist to lay the foundation for the therapeutic use of drugs. It is not his office to give minute directions to the internist concerning the administration of drugs. It is hardly necessary therefore, to discuss this chapter further.

R. A. H.

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Original Communications

PULSE WAVE VELOCITY AND ARTERIAL ELASTICITY IN ARTERIAL HYPERTENSION, ARTERIOSCLEROSIS, AND RELATED CONDITIONS*†

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THE elasticity of the arteries exerts a significant influence on the peripheral vascular resistance and on the blood flow. Other factors such as arteriolar resistance, cardiac output, circulating blood volume, and blood viscosity being constant, the more elastic the arteries the lower will be the systolic and pulse pressures, the less the work of the heart, and the more uniform the blood flow to the capillaries.

In man the arterial elasticity may be estimated in vivo from the pulse wave velocity since the less extensible the artery the greater is the pulse wave velocity. Bramwell and Hill¹ have shown that, barring variations in the blood flow, the extensibility of an artery may be expressed as follows:

$$\frac{\text{Percentage increase in volume}}{\text{per mm. Hg increase of pressure}} = \frac{12.7}{(\text{velocity in meters per second})^2}$$

The chief factors which alter the arterial elasticity, namely, (1) the condition and constitution of the arterial wall and (2) the effective pressure within the artery, have been recently discussed in some detail by Hallock² for normal subjects. The changes found by various observers in the pulse wave velocity in pathological conditions have been summarized in Table I.

We have made pulse wave velocity and oscillographic measurements in different parts of the body in an attempt to evaluate the arterial elasticity in hypertension and arteriosclerosis, in which conditions a priori the elastic properties of the vessels may be expected to be significantly

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TABLE I
OBSERVATIONS IN THE LITERATURE OF THE CHANGES IN THE PULSE WAVE VELOCITY IN HYPERTENSION, ARTERIOSCLEROSIS, AND OTHER PATHOLOGICAL CONDITIONS

AUTHOR	DATE	METHOD OF RECORDING PULSE WAVES	VELOCITY MEASURED	NORMAL VALUES (METERS PER SEC.)	HYPERTENSION	ARTERIOSCLEROSIS	OTHER CONDITIONS
Friberg	1912	Optical	Subclavian-radial.	Young controls 6.7-10.4 Average 8.2 (22 persons)	Increased in cases with highest blood pressure (nephritis). 8.6-14.5 Average 11.8 (9 cases)	Possibly slightly increased over controls of the same age. 7.0-10.1 Average 8.8 (14 young cases) Not proportional to the amount of palpable thickening but possibly greater in cases with poor pulsation.	
Ruschke	1912	Optical	Carotid-radial.	9	Increased 9-12 Average 10.4 (8 cases)		<i>Aortic and mitral insufficiency</i> —often slightly decreased and lower if decompensated (14 cases). <i>Nephritis</i> —10-14 (5 cases). <i>Scattered cases of anemia, chlorosis, tuberculosis, carcinoma, neurasthenia and hypotension</i> ; all rather low.
Münzer	1912	Kymograph	Upper arm to calf. Figures given for heart to calf.	9-12	Greatly increased. 14.5-23 (4 cases)	Increased in 1 of 3 cases reported. 7.2-16.5	<i>Scattered cases of mitral insufficiency, hemophilia, polycythemia</i> —normal. <i>Hypotension and aortic insufficiency</i> —low.

TABLE I—CONT'D

Silberman ⁶	1913	Kymograph	Upper arm to calf.	5.1 (1 person)	Variable on different days. 4.6-8.1 (2 cases)	Scattered cases of aortic insufficiency, septicemia, hyperthyroidism, gout, and gastric ulcer—very variable.
Laubry, Mougeot, and Giroux ⁷	1921	Kymograph Curves low	Subclavian-radial I. Femoral-tibial II. In some cases sub- clavian-femoral.	Young con- trols I. 7.9-9 II. 9-10 Compensated (5 cases). I. 11.6 II. 16.4 Insufficiency of left ventricle (10 cases). I. 10.0 II. 14.5 Blood pressures very high. When velocity does not follow systolic pressure it means insufficiency of left ventricle.	Three cases with hypertension reported. Aorta may be rigid and peripheral arteries relatively unaffected.	<i>Hypotension</i> —decreased velocity. <i>Pulsus alternans</i> —speed of feeble beat less than that of strong one. <i>Extrasystole</i> —decreased velocity in premature beats.
Branwell and Hills	1922	Hot wire sphygmograph	Carotid-radial.		Theoretically increased.	Scattered cases of aortic incompetence, heart-block, etc., of different ages. <i>Aneurysm</i> —velocity decreased.
Sandoe	1924	Optical	Apex-brachial I. Brachial-radial II. Apex-radial III. Apex-femoral IV. Femoral-dorsalis pedis V. Apex-dorsalis pedis VI.	I. 3.84 II. 7.66 III. 4.90 IV. 3.93 V. 8.44 VI. 5.61 (51 persons)	Two groups of patients: 1. Velocity increased in aorta but decreased in peripheral vessels. 2. Velocity increased in both central and peripheral vessels.	<i>Aortic regurgitation</i> —no change and no correlation with diastolic pressure. <i>Hyperthyroidism</i> —no change.

TABLE I—CONT'D

AUTHOR	DATE	METHOD OF RECORDING PULSE WAVES	VELOCITY MEASURED	NORMAL VALUES (METERS PER SEC.)	HYPERTENSION	ARTERIOSCLEROSIS	OTHER CONDITIONS
Beyer-holm ^{10, 11}	1927	Modified Ekg.	Carotid-radial.	90 persons 15-59 yr. 7.13	<i>Chronic nephritis</i> with hypertension but without arteriosclerosis —10.21.	Without hypertension —normal for the age of the group—7.52.	<i>Mitral insufficiency</i> —no great change in compensated cases.
				30-59 yr. 7.29			<i>Arrhythmia perpetua</i> —no difference in velocity of large and small waves.
				60+ yr. 7.82	<i>Hypertension with arteriosclerosis</i> —10.44.		<i>Scattered cases</i> of mediastinal tumor, diabetes, aortic aneurysm and pernicious anemia—no change.
							<i>Hyperthyroidism</i> —usually normal but may be increased.
Udel ¹²	1933	Optical	Subclavian-femoral. Femoral-radial. Time difference.	Young controls. 4.33-6.43 (Average 5.64) (20 persons)	High in persons without organic wall changes. 10.2-13.8; average 12.42. (6 cases; 52-81 yr.)	Somo increase over normals of the same age. Aortic sclerosis—9.00-15.5; average 11.28. (18 cases; 60-88 yr.) Femoral-radial time difference increased.	<i>Hypotension</i> —decreased.
					Increased in some cases but variable.	Without hypertension —increased in some cases but variable.	
Turner ^{13, 14}	1927 1934	Helium light	Carotid-radial.				

altered. This problem is of particular interest in connection with the question of increased tonus of the arteries in arterial hypertension, with or without arteriosclerosis.

METHOD

Pulse wave velocities were calculated from pulse wave tracings optically obtained by means of Frank segment capsules, as described by Lauber,¹⁵ Hallock,² and others. Pulsations were photographed on a bromide paper moving at approximately 50 mm. per second. The receiving instrument consisted of a shallow wooden cup covered with rubber dam on which, for small arteries, a cork pelote was mounted. It was often necessary to have the subject hold his breath in order to get an even record. Pulsations from the left subclavian, femoral, and dorsalis pedis arteries were usually recorded simultaneously. For each velocity measured, several records of three to six pulse waves each were read by means of a squared glass plate. Measurements were often repeated on a second or third day.

The extensibility of the brachial artery (right carotid-brachial velocity) was measured at different internal effective pressures (the diastolic minus the external pressure applied) by the application of a blood pressure cuff to the upper arm. By the formula of Bramwell, McDowall, and McSwiney¹⁶ the pulse wave velocity and the extensibility of the segment of artery under the cuff were calculated.

Anatomical measurements of the distance between the carotid and brachial arteries were made as described by Bramwell and Hill,¹ and between the subclavian and femoral arteries as described by Lauber.¹⁵ For the subclavian-brachial and the femoral-dorsalis pedis velocities, measurements were made directly on the surface of the body between the centers of the tambours. Satisfactory pulse wave velocities could be obtained only when the distances used were long enough to be measured with reasonable accuracy, as in the subclavian-femoral (aortic) and femoral-dorsalis pedis velocities.

Oscillometric determinations were made on the upper arm and the calf of the leg with a Boulitte modification of the Pachon oscillometer, using the two bags of the cuff as a single bag system. The cuff pressure has been plotted against arbitrary units of oscillation.

The patients studied were recumbent and had rested until their blood pressures were essentially constant. Usually they were in a basal condition, but a few had had breakfast two to three hours before the test. The patients studied included (1) *controls*, with little or no apparent arteriosclerosis, who were recovering from diseases not involving the cardiovascular system; (2) patients with marked *arteriosclerosis*, as indicated by clinical and x-ray examination, but with normal blood pressures; and (3) patients with *arterial hypertension* with little or no arteriosclerosis, whose circulatory state was normal at the time of the test and

whose blood pressures had remained elevated after entry. In our experience patients with normal blood pressure in whom a diagnosis of advanced sclerosis can be made with certainty are not very common. In order to evaluate certain aspects of the problem, we also conducted studies on a number of patients with postural hypotension, aortic regurgitation, hemiplegia, and polycythemia, as well as on hypertensive patients whose blood pressures were low at the time of the tests, although they had previously been high for a considerable period.

RESULTS

I. Pulse Wave Velocity

Averages of pulse wave velocity determinations made on each patient have been summarized in Tables II to VII. The subclavian-brachial or

TABLE II
THE PULSE WAVE VELOCITY IN CONTROL SUBJECTS AND IN PATIENTS WITH ARTERIOSCLEROSIS

NO.	SEX	AGE	DEGREE OF ARTERIO- SCLERO- SIS	ARTERIAL BLOOD PRESSURE (MM. HG)	PULSE PRESSURE (MM. HG)	PULSE WAVE VELOCITY		
						SUB- CLAVIAN- FEMORAL (METERS PER SEC.)	FEMORAL- DORSALIS PEDIS (METERS PER SEC.)	CAROTID- BRACHIAL (METERS PER SEC.)
Controls								
81	F	18	-	111/63	48	3.42	7.98	4.13
103	M	18	-	124/60	64	4.26	7.86	---
5	F	27	-	105/73	32	5.18	9.62	---
91	M	29	-	107/64	43	5.31	8.46	5.21
9	F	30	-	106/59	47	6.00	8.18	6.18
8	M	31	-	108/63	45	5.30	9.79	5.50
86	M	33	-	118/70	48	4.92	11.14	---
10	F	35	-	104/64	40	5.10	8.69	5.71
26	M	45	±	108/60	48	5.55*	11.11	6.12
22	M	48	-	134/84	50	7.28	9.87	8.85
17	M	49	-	114/70	44	7.07*	9.42	6.48
19	M	52	-	103/65	38	7.73*	9.19	6.42
72	F	56	±	140/76	64	7.06	11.41	7.60
71	M	65	+	109/72	37	7.79	14.30	9.01
59	M	65	+	122/75	47	7.73	12.14	7.06
25	M	73	±	130/66	64	8.33	9.46	6.77
58	M	79	-	127/61	66	10.03	10.68	6.80
Patients With Arteriosclerosis								
34	M	50	++	114/70	44	6.80	8.75	6.40
35	F	64	++	120/60	60	8.24	12.99	6.09
29	M	65	++++	112/76	36	9.22	10.42	6.45
28	M	70	++++	128/75	53	7.17	10.70	7.36
30	M	70	+++	133/66	67	9.10	12.08	7.82
55	M	74	+++	116/74	42	8.49	11.29	6.30
33	M	75	++	134/63	71	8.96	10.15	8.24
32	M	76	++	146/68	78	9.76	9.84	6.29
			or					
			+++					
36	M	76	++	113/64	49	9.65	13.30	7.32
			or					
			+++					

*Carotid-femoral pulse wave velocity.

carotid-brachial pulse wave velocities are based on fewer determinations (one or two) than the other velocities and are therefore somewhat less accurate. The pulse wave velocity may vary by as much as 10 to 15 per cent in the same patient on different days. Pulse wave velocities in young control subjects from eighteen to thirty-five years old (subclavian-femoral 3.42 to 6.00 meters per second, average 4.94; femoral-dorsalis pedis 7.98 to 11.14, average 8.96) agreed with those in the literature in which anatomical measurements were made by the same methods.^{12, 17, 18} The data indicate, as Bazett and others have shown, that the pulse wave travels faster in the peripheral arteries than in the aorta.

Changes in Arterial Elasticity With Changes in the Arterial Wall But Without Changes in Blood Pressure.—a. Age: The pulse wave velocity of the aorta (subclavian-femoral) increased from approximately 5 meters

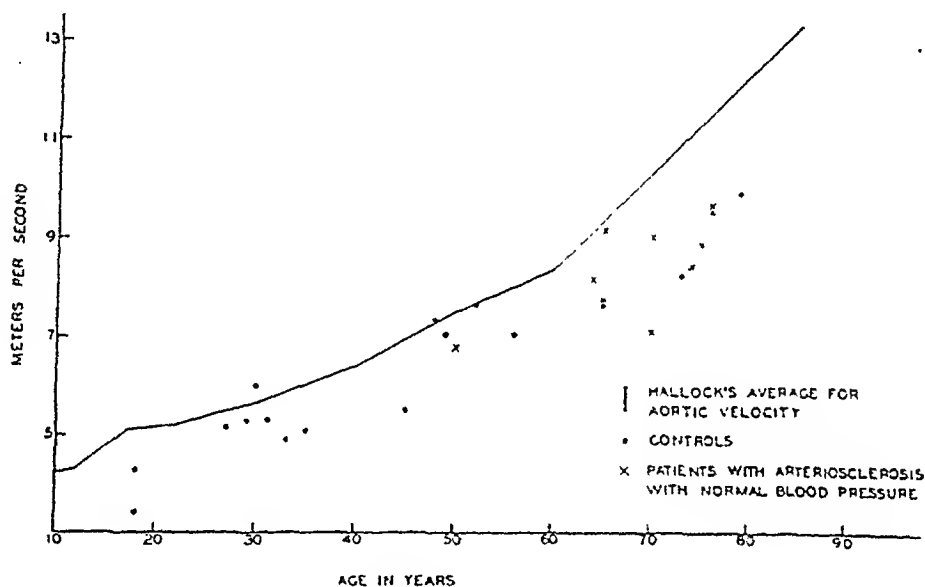


Chart 1.—Relation of the subclavian-femoral (aortic) pulse wave velocity to age in control subjects and in patients with arteriosclerosis.

per second at twenty-five years to 8 or 9 meters at seventy years (Table II and Chart 1). The points fall close to Hallock's² average curve for a large series of similar values but are on the average somewhat lower, probably due to the difference in the method of anatomical measurement. The values for the carotid-brachial and femoral-dorsalis pedis velocities (Chart 2) showed a general increase with age, but the spread of points was wider, especially in the femoral-dorsalis pedis velocity. This may be due either to technical difficulties of recording the dorsalis pedis pulsations or to variations in tone in the smaller arteries. To what extent the increase in the velocity with age is due to the blood pressure increase with age is not clear, but the effect of this factor is probably slight. The results agree with morphological findings that

after the early forties there is a progressive loss of elasticity of the arteries, as shown by a thickening and hardening as well as a marked stretching of the walls of the vessels.¹⁹

b. *Arteriosclerosis*: The results on patients with arteriosclerotic changes in the medium-sized arteries, which were definitely palpable or visible by x-ray, but with normal blood pressures (Table II and Charts 1 and 2), showed that the pulse wave velocities were not abnormally increased but fell directly in line with the controls for the same age group. In fact, Case 28, a patient with extreme Mönckeberg calcification which was easily seen on x-ray, showed rather low pulse wave velocities.

Results in the literature on the effect of arteriosclerotic changes on the pulse wave velocity are variable and hard to evaluate (Table I).²⁰ Sands⁹ has pointed out that tortuosity, especially in the peripheral ves-

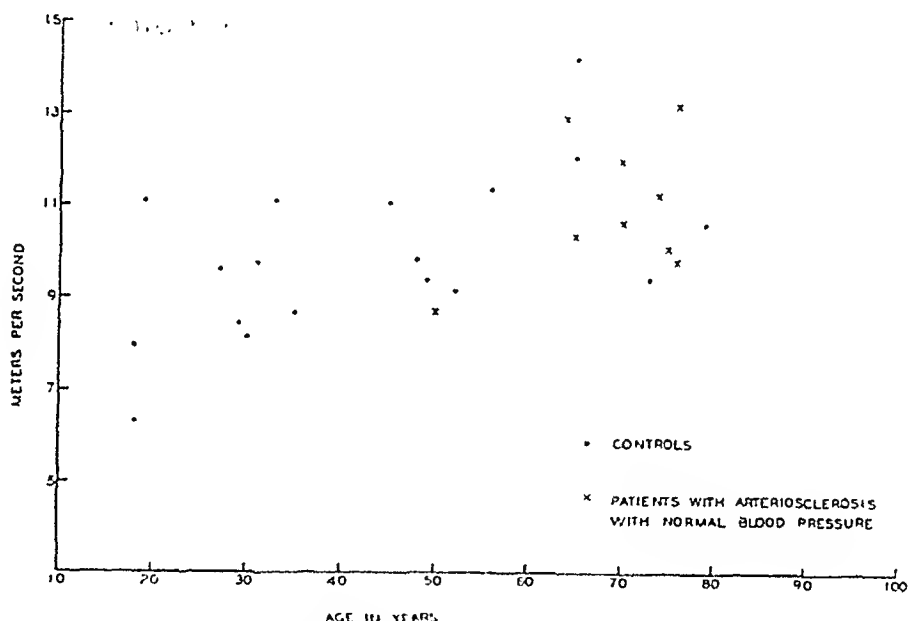


Chart 2.—Relation of the femoral-dorsalis pedis pulse wave velocity to age in control subjects and in patients with arteriosclerosis.

sels, may be an important factor in keeping the pulse wave velocity low in such cases. In Case 28 with low velocities, however, x-rays of the arms and legs showed the arteries to be practically straight. Other factors, such as the diameter of the lumen and the thickness of the arterial wall, may also have a variable influence.

e. *Effect of Preexisting Hypertension*: The arterial velocities of four patients who had had hypertension for some years, but whose blood pressures were lowered to normal levels on account of decompensation or rest in bed, were elevated slightly, if at all, above the values for controls of the same age (Table III). The thickening of the arterial wall, which has been demonstrated by others¹⁹ and which is assumed to be present in the arteries of these patients, is not reflected in arterial elasticity measurements.

TABLE III

THE PULSE WAVE VELOCITY IN PATIENTS WITH PREEXISTING HYPERTENSION

CASE	AGE	DEGREE OF ARTERIO- SCLEROSIS	ARTERIAL BLOOD PRESSURE (MM. HG)	PULSE WAVE VELOCITY		
				SUBCLAVIAN- FEMORAL (M./SEC.)	FEMORAL- DORSALIS PEDIS (M./SEC.)	CAROTID- BRACHIAL (M./SEC.)
66	38	+	109/62	6.48	10.22	7.37
104	41	+	135/90	6.44	9.68	7.25
67	50	+	138/76	7.86	10.93	8.00
68	62	+	130/72	9.74	11.72	8.26

Changes in Arterial Elasticity With Changes in Blood Pressure.—

a. *Arterial Hypertension:* In patients with hypertension but with little or no clinical evidence of arteriosclerosis, the pulse wave velocity was increased appreciably over controls of the same age (Table IV). A graphic representation of the relation of the pulse wave velocity to the blood pressure in these patients is complicated by the change in the

TABLE IV

THE PULSE WAVE VELOCITY IN PATIENTS WITH ARTERIAL HYPERTENSION

NO.	SEX	AGE	DEGREE OF ARTERIO- SCLEROSIS	ARTERIAL BLOOD PRESSURE (MM. HG)	PULSE PRESSURE (MM. HG)	PULSE WAVE VELOCITY		
						SUB- CLAVIAN- FEMORAL (METERS PER SEC.)	FEMORAL- DORSALIS PEDIS (METERS PER SEC.)	CAROTID- BRACHIAL (METERS PER SEC.)
69	F	16	+	182/130	52	7.61	13.57	6.60
50	F	31	—	190/120	70	8.08*	10.62	6.54
92	F	32	+ or ++	220/150	70	11.39*	17.17	9.18
60	M	33	+	148/112	36	13.65	13.28	7.56
51	F	34	—	165/112	53	8.20	10.18	7.04
99	M	37	+	158/110	48	7.36	—	—
49	M	38	—	150/112	38	6.40	11.52	8.20
62	F	38	—	250/145	105	13.02	14.71	7.90
44	F	38	+	160/109	51	12.61	11.58	7.54
100	F	39	—	197/116	81	7.36	—	—
61	F	40	—	190/108	82	9.64	13.08	8.50
73	F	40	+	180/112	68	9.89	13.82	8.55
40	M	44	—	196/120	76	10.72	14.86	6.42
85	M	44	—	202/102	100	10.54	11.32	—
87	F	49	—	214/114	100	14.07	12.99	—
75	M	49	+	192/108	84	10.75	9.28	—
76	F	50	+	206/ 74	132	17.02	14.26	12.02
102	F	52	+	211/103	108	10.13	12.57	—
78	F	53	+ or ++	210/124	86	12.74	13.45	—
47	M	54	+ or ++	160/104	56	9.33	12.26	7.10
70	M	54	+	170/110	60	9.43	12.95	—
48	F	56	+	240/134	106	13.57	13.44	7.58
54	F	58	—	212/110	102	9.92	11.42	6.81
105	F	60	—	208/109	99	15.04*	15.35	10.77
93	F	63	+	180/105	75	11.70	10.32	—
46	F	65	—	190/118	72	13.35	12.48	10.80
45	F	65	+	200/ 85	115	9.48	9.66	6.26
11	F	68	—	175/ 85	90	10.12	8.18	9.20
84	F	69	+	188/ 80	108	15.70	12.39	8.58
53	M	77	±	176/102	74	11.00	13.28	—

*Carotid-femoral pulse wave velocity.

pulse wave velocity with age. If, however, the results for young controls and young hypertensives (ages sixteen to thirty-nine years) are plotted, as well as those for older controls and hypertensives (ages 40 to 77 years), it may be seen that the pulse wave velocity of the aorta in the hypertensive patients ranged considerably above that of controls, although showing a wide spread of points. This was true whether the aortic (subclavian-femoral) velocity was plotted against the systolic, diastolic, mean or pulse pressures (Chart 3). The femoral-dorsalis pedis (Chart 4) and the carotid-brachial velocities were also somewhat increased. The decrease in distensibility due to increase in blood pressure in older patients with hypertension is more apparent in the aorta than in the more muscular peripheral arteries.

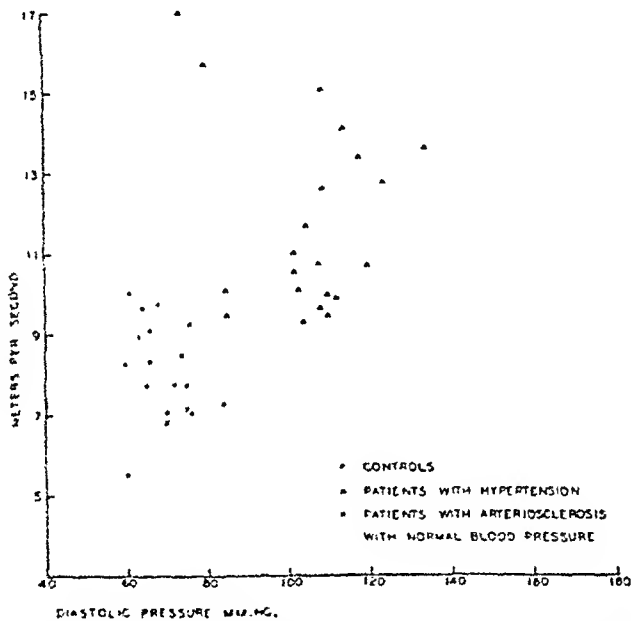


Chart 3.—Relation of subclavian-femoral aortic pulse wave velocity to diastolic blood pressure in older patients (forty to seventy-seven years).

b. *Effect of Vasodilatation:* Since nitrites are known to relax the arterial and arteriolar systems and to lower the blood pressure temporarily, we have given from 2 to 5 grains of sodium nitrite by mouth to ten patients with hypertension and have followed the blood pressure and pulse wave velocities for one to two hours. In all but two patients the systolic blood pressure fell from 20 to 50 mm. Hg as the result of the drug, whereas the diastolic pressure fell to a lesser extent (0 to 20 mm. Hg). Of the eight patients with a blood pressure fall, three showed a fall of over 2 meters per second in the femoral-dorsalis pedis velocity and two others a slight fall. In two cases the subclavian-femoral velocity rose temporarily, and in one case it fell slightly. In the light of these results one cannot consider the fall in systolic pressure as the only significant factor affecting the pulse wave velocity in these cases. Lauber¹⁵ found

a fall in the subclavian-femoral velocity in two cases with a marked fall in blood pressure due to nitroglycerin. Turner and Sodeman,²⁶ however, mention two instances in which reducing the pressure in hypertensive patients by nitrites actually increased the pulse wave velocity and conclude that changes in arterial tone, largely independent of the blood pressure, may greatly influence the pulse wave velocity in the brachial and radial arteries.

c. *Postural Hypotension*: In order to test the effect of blood pressure, without change in the constitution of the artery, determinations were made on the carotid-brachial and carotid-radial velocities in two cases of postural hypotension. The arm was kept at heart level and measurements were made with the patients lying and standing. Both

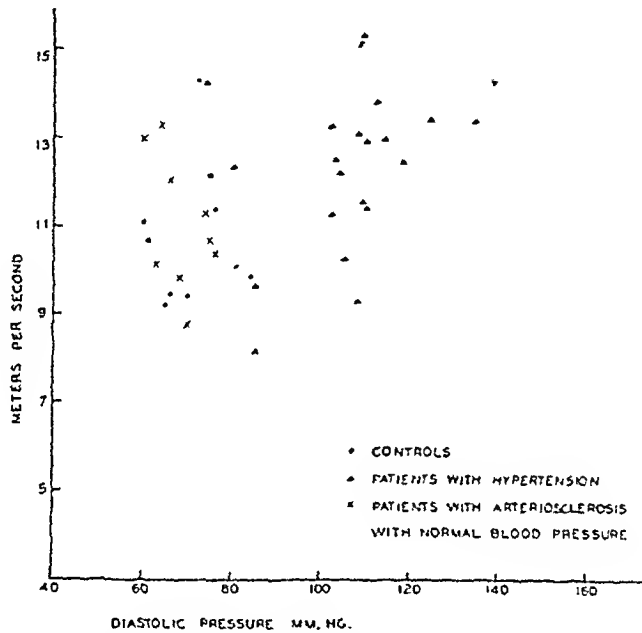


Chart 4.—Relation of femoral-dorsalis pedis pulse wave velocity to diastolic blood pressure in older patients (forty to seventy-seven years).

cases showed a fall in pulse wave velocity accompanying the fall in blood pressure on standing, whereas two controls showed no significant fall in either blood pressure or pulse wave velocity (Table V).

TABLE V

THE PULSE WAVE VELOCITY IN THE HORIZONTAL AND VERTICAL POSITIONS IN CONTROLS AND IN PATIENTS WITH POSTURAL HYPOTENSION

NO.	ARTERIAL BLOOD PRESSURE		PULSE WAVE VELOCITY			
			CAROTID-BRACHIAL		CAROTID-RADIAL	
	LYING (MM. HG)	STANDING (MM. HG)	LYING (M./SEC.)	STANDING (M./SEC.)	LYING (M./SEC.)	STANDING (M./SEC.)
<i>Controls</i>						
110	102/60	98/58	5.84	5.76	7.44	8.49
111	102/64	102/69	5.25	5.38	6.68	6.54
<i>Patients With Postural Hypotension</i>						
94	113/75	62/52	9.29	6.31	9.76	7.96
11	168/82	68/56	9.20	5.88	10.08	7.78

d. *Aortic Regurgitation:* We have measured the pulse wave velocities in six cases of aortic regurgitation and present them to demonstrate the effect of a lowered diastolic pressure (Table VI). All but one have a lowered aortic (subelavian-femoral) velocity. The third case, in which the femoral-dorsalis pedis velocity was also measured, showed a low leg velocity, although the systolic pressure in the leg was about 100 mm. Hg higher than that in the arm. The low velocity must be considered

TABLE VI
THE PULSE WAVE VELOCITY IN PATIENTS WITH AORTIC REGURGITATION

NO.	AGE	ARTERIAL BLOOD PRESSURE (MM. HG)	PULSE WAVE VELOCITY		
			SUBCLA- VIAN- FEMORAL (M./SEC.)	FEMORAL- DORSALIS PEDIS (M./SEC.)	CAROTID- BRACHIAL (M./SEC.)
96	22	176/56	3.92	---	---
95	25	132/43	4.96	---	---
57	28	160/15	3.70	7.34	---
97	40	101/70	3.92	---	---
98	42	147/32	3.57	---	---
82	58	140/50	6.09	9.69	5.70

an expression of a lowered peripheral resistance and a mean pressure which is not elevated. These results differ somewhat from those of Sands,⁹ who concludes that aortic regurgitation without changes in the vessel wall probably has no effect on the pulse wave velocity.

Other Factors Which May Alter the Pulse Wave Velocity.—a. *Hemiplegia:* Owing to the fact that in hemiplegia there is decreased vascular tone on the paralyzed side,²¹ the pulse wave velocity was determined on the two sides in five cases of hemiplegia. These cases were measured at least ten days after the hemiplegia took place. The subelavian-femoral values on the two sides checked, as would be expected since the same vessel, the aorta, was chiefly involved. The velocities in the two arms and legs did not vary significantly or consistently. It is apparent (Table VII) that the pulse wave velocity as here measured does not detect any tonus differences on the two sides.

TABLE VII
THE PULSE WAVE VELOCITY* ON THE TWO SIDES IN PATIENTS WITH HEMIPLEGIA

CASE	SUBCLAVIAN OR CAROTID-FEMORAL		FEMORAL- DORSALIS PEDIS		SUBCLAVIAN OR CAROTID-BRACHIAL	
	NORMAL	PARALYZED	NORMAL	PARALYZED	NORMAL	PARALYZED
22	7.28	7.65	9.87	11.10	8.31	7.71
24	6.20	6.10	9.10	10.30	---	7.06
46	13.35	13.86	12.48	12.26	10.80	---
34	6.80	5.98	8.75	8.11	6.40	6.36
23	---	13.47	11.23	11.63	6.38	6.26

*Pulse wave velocities are expressed in meters per second.

b. *Polycythemia:* We had occasion to measure the velocities in two cases of polycythemia. The values for the subelavian-femoral and femoral-dorsalis pedis velocities were low for the age and blood pres-

sure of the patients. In the original formula² worked out experimentally for the passage of a pulse wave, the velocity is inversely proportional to the square root of the density of the blood. Although this factor probably is not ordinarily important, a great increase in cells, such as is here represented, may lower the velocity.

II. Arterial Extensibility Curves

Composite extensibility curves for control subjects and patients with hypertension and arteriosclerosis have been plotted in Chart 5. The value at the extreme right on each curve represents the extensibility at the diastolic pressure. As the pressure cuff on the arm was inflated, the effective pressure in the brachial artery was lessened, the pulse wave velocity gradually fell, and the extensibility increased, rising quite sharply as the diastolic pressure was applied. It should be noted that the normal curve plotted from the work of Hemingway, McSwiney, and Allison²² was obtained from the carotid-radial instead of the carotid-

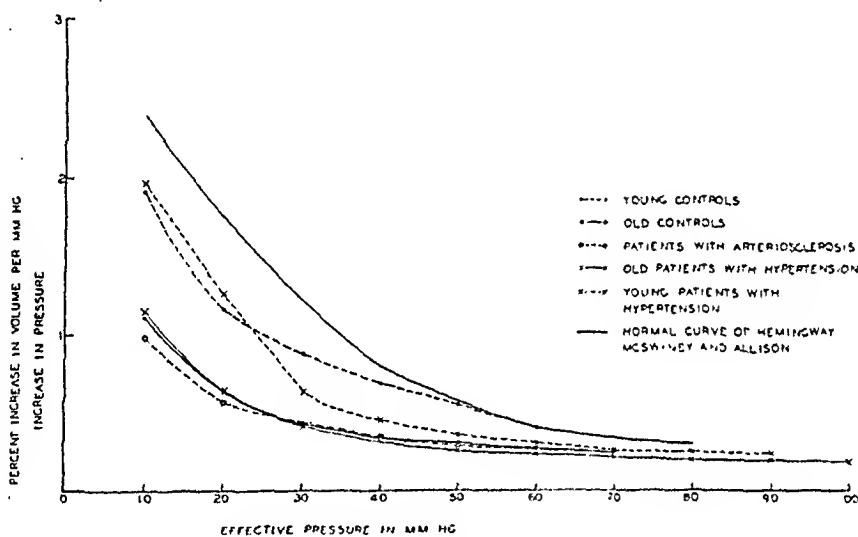


Chart 5.—Extensibility of brachial artery in control subjects and in patients with arteriosclerosis and hypertension.

brachial velocity. They also used a wide cuff covering a large part of the arm, instead of an ordinary blood pressure cuff. Our young normals did not include any of the "hyperextensible" individuals mentioned by these workers.

From the curves on the chart it is seen that in agreement with the pulse wave velocity the extensibility of the brachial artery was decreased with age but was not further changed in persons with palpable brachial and radial arteries. In one case with an extreme degree of medial calcification the extensibility curve, although not especially low, was exceedingly flat and did not rise above 0.7 even at zero effective pressure. This probably indicates that the artery was not collapsed, even when a pressure above the diastolic was applied. In older patients with arterial hypertension the extensibility was low, since both the diastolic pressure and the velocity were elevated. When the internal effective pressure was reduced, however, the curve was practically identical with that of

other patients of the same age group without hypertension. The curves of young patients with hypertension were more variable than those of young control subjects and the average curve was a different shape, being somewhat lower along the middle (Chart 5).

III. Oscillometric Curves

Friedlander²³ has pointed out that normally oscillometric readings are not greatly influenced by age. Our normal oscillograms of the upper arm and calf were similar to those shown by Friedlander although the point of maximum oscillation (MOP) was slightly lower. The curve for the hypertensive group, as would be expected, was shifted to the right. In both the upper and the lower extremities the MOP occurred at much higher levels. The unit height of the oscillations was also high. Certain of our cases with marked arteriosclerosis showed relatively low leg curves, but the results varied considerably and seldom fell definitely into the groups described by Friedlander²³ or Finck.²⁴ In one case of Mönckeberg's sclerosis the arm and leg curves were both very low. The curves on the two sides in patients with hemiplegia did not differ to a greater extent than in normal subjects.

DISCUSSION

The data presented indicate that the changes in the arteries which take place with age are more significant in modifying the pulse wave velocity and extensibility of the arteries than palpable arteriosclerotic changes in the arterial wall. It is apparent that in individual cases of arteriosclerosis the measurements of the pulse wave velocity are not clinically significant as a measure of the degree of arterial change, even when the internal effective pressure is reduced to a constant figure.

The data obtained do not explain the discrepancy that exists in arteriosclerosis between the clinical manifestations and x-ray findings, on the one hand, and the pulse wave velocities, on the other hand. An explanation is suggested, however, by the histological findings, which indicate that atheromatous deposits in the intima and media are usually irregularly scattered and are imbedded in or attached to the otherwise normal structures of the arteries. It appears that as long as the arterial system is not diffusely involved and the bulk of the structure remains normal, there will be no change in pulse velocity. When, on the contrary, the vascular change is diffuse, as occurs in the aging process, alteration in the velocity results, in spite of the fact that clinical and x-ray examinations fail to demonstrate changes. It should also be emphasized that clinical symptomatology of arteriosclerosis depends on the location of focal vascular lesions rather than on the diffuseness of the process. A single cholesterol plaque over the intima of the coronary, cerebral, and certain other arteries will precipitate intense and persistent symptoms and grave alterations of the bodily function, in spite of the fact that the bulk of the arterial system and pulse wave velocity remain

normal. Thus a detailed consideration of the known facts concerning the histopathology and clinical manifestations of arteriosclerosis offers an explanation for the apparent discrepancy existing between the clinical picture of, and the pulse wave velocities in, arteriosclerosis.

As pointed out by Beyerholm,¹⁰ the blood pressure may influence the pulse wave velocity more than the anatomical nature of the vessel walls and the dimensions of the arteries. Conclusions based on observations on normal human beings vary, however, as to whether the velocity is related to the systolic, diastolic, or mean blood pressure.^{9, 17, 18, 25, 26} Hallock² points out that certain of this work is not valid since the age factor has not been eliminated. High blood pressure mechanically changes the elasticity of the arteries and thus increases the pulse wave velocity. Such a change in the pulse wave velocity, however, is not an indication of a primary organic change in the vascular structure. This is borne

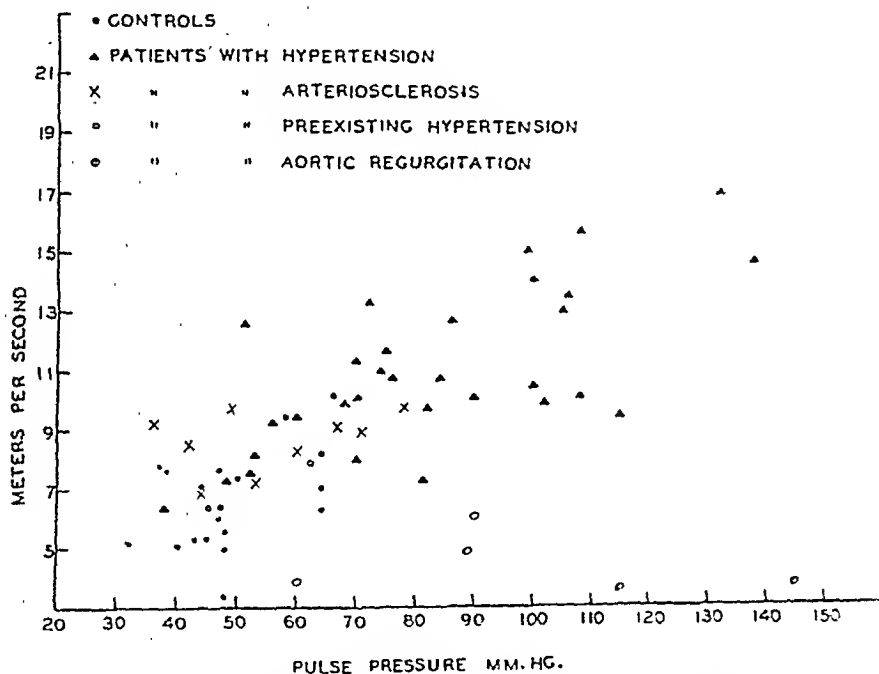


Chart 6.—Relation of subclavian-femoral (aortic) pulse wave velocity to pulse pressure.

out by the fact that following the spontaneous return of the pressure to normal, the values of the pulse wave velocity usually reach normal standards. Furthermore, extensibility curves of the arteries do not indicate changes in the arterial wall, aside from changes in blood pressure.

It is of interest to ascertain as far as possible from the data at hand to what extent pulse pressure is related to the arterial elasticity, as indicated by the pulse wave velocity. In Chart 6 we have plotted in all cases, regardless of age, the aortic (subclavian-femoral) pulse wave velocity against the pulse pressure. In general, as the extensibility decreases (i.e., as the velocity increases, whether due to arterial change or to increased pressure), the pulse pressure increases. The cases of aortic regurgitation form a marked exception. Regardless of the height of the systolic pressure, the velocity remains low, presumably due to the low

diastolic pressure and lowered peripheral resistance. Two patients have been studied who had high systolic pressures associated with normal diastolic pressures, so that the pulse pressures were unusually high (132 to 138 mm. Hg). There was no evidence of aortic insufficiency. These patients had exceedingly high pulse wave velocities, which are represented by the two points at the extreme upper right corner of the chart. This is the type of case in which one would expect to have greatly increased rigidity in the aorta without markedly increased peripheral resistance, as is borne out by velocity measurements.

When the femoral-dorsalis pedis or carotid-brachial velocity is plotted in a similar way, the spread of points is wide, and the relationship to pulse pressure is less apparent. One may expect, therefore, that the conditions in the aorta, which contains considerable elastic tissue, may have more part in determining the pulse pressure than conditions in the smaller, more muscular arteries. The relation of the pulse pressure to arterial elasticity in hypertension will be discussed in the succeeding paper.

SUMMARY

1. The arterial elasticity in normal subjects and in patients with arteriosclerosis, arterial hypertension, and other conditions with alterations in the arterial pressure was estimated from measurements of the subclavian-femoral (aortic), femoral-dorsalis pedis (leg) and carotid or subclavian-brachial (arm) pulse wave velocities, as well as from studies of the arterial extensibility and oscillometric curves.

2. The pulse wave velocity increased with age. Values on patients with clinical and x-ray evidence of marked thickening and calcification of the arteries but with normal blood pressures fell on the curve for controls of the same age group. The extensibility curves of the normal and arteriosclerotic groups were essentially similar. Patients with histories of hypertension of several years' duration, but with normal blood pressures at the time of the test, had essentially the same pulse wave velocities as controls of the same age.

3. Patients with arterial hypertension showed increased pulse wave velocities. The data obtained did not reveal whether this change follows the systolic, diastolic, or pulse pressure most closely. The pulse wave velocity of the aorta was often more affected by blood pressure or pulse pressure changes than was that of the arteries of the extremities.

4. In hemiplegia, tonns differences in the arteries of the two sides were not indicated by differences in the pulse wave velocity.

5. In some cases of arteriosclerosis, oscillometric curves on the calf of the leg were low as compared with those of the upper arm, but the results were quite variable. In patients with arterial hypertension, oscillometric curves were shifted to the right, and the maximal oscillometric phase was often high.

6. While measurements of pulse wave velocities and oscillometric curves give significant information on the physiological aspects of arte-

rial elasticity in health and in disease, no practical conclusions can be drawn from these measurements on an individual case. An apparent discrepancy exists between structural characteristics of the peripheral arteries in arteriosclerosis, as estimated by clinical and x-ray examination, and the results obtained with measurements of the pulse wave velocities. An explanation for this apparent discrepancy is offered.

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THE RELATION OF ARTERIAL PULSE PRESSURE TO THE HEMODYNAMICS OF ARTERIAL HYPERTENSION*†

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IN PATIENTS with arterial hypertension the pulse pressure varies over an unusually wide range, and high pulse pressure without valvular defect is a common finding. The factors responsible for such a high pulse pressure are not well understood. This investigation was undertaken to ascertain whether certain factors controlling the circulation can be related to the height of the pulse pressure in patients with arterial hypertension.

The chief factors which determine the pulse pressure are necessarily those which influence the height of the systolic and diastolic blood pressures. Wiggers¹ has demonstrated, by means of an artificial circulation machine, the influence of the following factors on the pulse pressure: (1) *Peripheral resistance*. Theoretically an increase in the peripheral resistance alone may be expected to elevate both the systolic and the diastolic blood pressures. Since the outflow of blood at the periphery is relatively less during diastole than during systole, the diastolic pressure is raised to a greater extent than the systolic and the pulse pressure decreases. (2) *Systolic discharge*. Augmented systolic discharge may be expected to increase both the systolic and the diastolic pressures. Since in this condition the outflow of blood is relatively greater during diastole than during systole, the systolic pressure increases more than the diastolic and the pulse pressure increases. Thus increased stroke volume is often associated with an increase in the pulse pressure. (3) *Arterial elasticity*. Decreased arterial elasticity alone elevates the systolic pressure and decreases the diastolic pressure. As Wiggers¹ has pointed out, "This change in systolic pressure is due to the fact that the whole arterial system accommodates less liquid during systolic ejection hence requires a greater pressure to force out the same volume." Owing to the higher systolic pressure the amount of blood flowing away at the periphery is greater during diastole, with the result that the diastolic pressure falls. The mean pressure changes but little.

Under special conditions the heart rate and blood volume must also be considered as affecting the pulse pressure. "At a constant peripheral resistance and a constant volume of ejection a sudden increase in heart rate leads to an . . . increase in systolic and diastolic pressures, the

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diastolic pressure . . . rises more than the systolic, and the pulse pressure decreases."¹ Increasing the circulating blood volume by infusion of saline or heparinized blood increases the pulse pressure. Wiggers¹ also discusses the bearing of these factors on arterial hypertension.

As has been pointed out by Weiss and Ellis,² the influence of these factors in the body is complicated by the fact that a number of regulatory mechanisms are active. Thus in order to obtain a knowledge of the dynamics of the circulation in hypertension, it is necessary to study simultaneously several of the factors which influence the pulse pressure. For this purpose we have made measurements of several of the circulatory functions in hypertensive cases with high, normal, and low pulse pressures.

METHOD

A study of the cardiac output, blood volume, vital capacity, cardiac size, pulse wave velocity, and oscillometric curves has been made on twenty-five cases of arterial hypertension. Patients whose blood pressures had remained elevated after a rest period of several days in the hospital were selected. None of the patients had valvular heart disease or exhibited clinical or laboratory evidence of circulatory failure at the time determinations were made. The majority, fifteen patients, suffered from "primary" arterial hypertension without obvious kidney involvement. In the rest various degrees of kidney impairment existed, as was indicated by kidney function tests.

The circulatory measurements were made with the patients in basal condition. The arterial blood pressure was estimated by the Riva Rocci method, using a mercury sphygmomanometer. The acetylene method of Grollman³ was used for measurement of the cardiac output. The patient was in the sitting position, and two expiratory samples were taken for each determination. The samples were obtained after the sixth and eighth breaths, or at approximately 19 and 25 seconds. Patients were previously trained in the respiratory gymnastics. Care was always taken to adjust the volume of gas rebreathed so that the bag was completely emptied with each respiration. The Benedict-Roth method was used in calculating the oxygen consumption. In all cases duplicate cardiac output determinations were made on the same day. Usually this was repeated one or more times within the next few days. The circulating blood volume was measured according to the technique described by Keith, Rowntree and Geraghty.⁴ The mean velocity of the entire circulation was calculated by dividing the circulating blood volume by the cardiac output per minute. Seven-foot x-ray pictures of the heart were taken for cardiac measurements. Pulse wave velocities were obtained optically from pulse curves from the subclavian, femoral, and dorsalis pedis arteries. Anatomical measurements of the length of the arteries were made as described in the preceding paper.⁵ The calculation of the cardiac output from the pulse wave velocity was carried out by the method of Broemser and Ranke,⁶ which has been more specifically applied to man by Lauber.⁷ The results thus obtained were compared with those with the acetylene method. Oscillometric curves were constructed from measurements made on the arm and leg by means of a Pachon oscillometer with a single cuff system, as previously described.⁵

In order to throw light on the problem as to whether or not *in vivo* the lumen, and hence the volume, of the larger arteries is changed in arterial hypertension, the diameters of the radial and ulnar arteries in an additional group of seven patients with hypertension have been compared with those in seven control subjects. An attempt was also made to measure the arterial lumen in the lower ex-

TABLE I
THE RELATION OF THE PULSE PRESSURE TO THE CARDIAC OUTPUT IN PATIENTS WITH ARTERIAL HYPERTENSION

CASE	AGE	ARTERIAL BLOOD PRESSURE			HEART RATE	OXYGEN CONSUMPTION (C.C. PER MIN.)	CARDIAC OUTPUT BY ACETYLENE METHOD			BLOOD VOLUME		MEAN VELOCITY (SEC.)	VITAL CAPACITY	
		SYSTOLIC (MM. HG.)	DI-ASTOLIC (MM. HG.)	PULSE PRESSURE (MM. HG.)			(L. PER MIN.)	(SQ. METER)	(C.C. PER BEAT)	(L.)	(C.C. PER KG.)		(L.)	(SQ. METER)
156	46	246	128	118	66	262	4.02	2.20	61	5.84	67.7	87	2.10	1.15
155	82	190	79	111	60	228	3.80	2.08	63	5.32	75.5	84	3.60	1.98
100	39	225	121	104	86	221	4.30	2.64	50	4.41	71.9	62	3.20	1.96
101	34	240	140	100	72	266	3.66	2.44	51	---	---	---	2.10	1.40
108	92	181	91	90	64	235	3.78	2.39	59	5.00	87.3	79	---	---
83	59	250	160	90	80	266	3.89	2.43	48	4.63	82.7	72	2.20	1.38
154	81	161	76	85	74	187	3.30	2.11	44	3.74	72.8	68	2.80	1.80
105	60	200	117	83	72	221	3.84	2.38	53	3.88	63.2	61	1.80	1.12
151	69	178	96	82	72	235	4.00	2.75	55	3.71	75.6	56	2.15	1.48
13	57	176	96	80	80	204	3.45	2.18	43	4.50	75.6	78	2.20	1.39
153	59	188	108	80	90	221	3.14	1.92	35	4.02	62.7	77	1.90	1.17
150	57	198	124	74	104	221	2.34	1.36	23	3.81	50.3	98	1.80	1.05
107	40	226	148	78	77	230	3.95	2.35	51	3.88	63.3	59	3.20	1.90
152	28	244	175	69	86	394	5.12	3.15	59	4.94	92.0	58	2.20	1.36
78	51	192	128	64	76	190	2.96	1.82	39	4.45	67.6	90	1.80	1.11
40	44	197	136	61	68	270	4.20	2.56	62	---	---	---	4.20	2.55
92	32	220	162	58	92	238	3.42	2.50	37	4.70	105.5	82	2.90	2.12
51	34	167	109	58	66	171	2.92	1.84	44	4.50	77.3	92	3.20	2.01
47	54	162	107	55	80	266	3.36	2.11	42	6.13	110.3	109	3.80	2.39
99	37	175	125	50	70	272	5.43	2.93	78	6.11	84.0	68	4.20	2.27
106	32	138	95	43	75	278	3.45	1.80	46	5.60	71.2	97	4.00	2.08
44	37	164	122	42	88	218	3.81	2.77	43	4.43	87.8	70	2.60	1.89
60	34	159	121	38	80	235	3.45	2.04	43	5.42	88.9	94	3.10	1.84
69	34	152	118	34	84	232	4.36	3.09	52	3.34	74.2	46	3.00	2.12
12	60	141	110	31	80	225	2.85	1.68	36	4.78	69.2	100	2.30	1.35

tremities, but here the vessels were not clearly visualized. Arteriograms were obtained with the injection of freshly prepared 20 per cent sodium iodide solution under sterile precautions. A 23-gauge hypodermic needle was used for the intra-arterial injection. In order to avoid the influence of pain on the arterial tonus, not only the site of injection, but also the sensory nerves of the forearm were infiltrated with a 2 per cent novocaine solution. All x-ray pictures were taken under standard conditions, the distance between the tube and the forearm being 71 cm. The x-rays were taken about one to two seconds after the beginning of the injection and while it was still in progress. The width of the arterial shadow was estimated to 0.1 mm. with a draftsman's compass on a linear millimeter scale. A certain degree of magnification of the actual diameter occurred on the shadow. Taking into consideration the distance of the x-ray tube and of the artery from the plate, the actual diameter was computed mathematically. It has been estimated that such computation would allow for a maximal possible error of 0.3 mm.

RESULTS

The Relation of Pulse Pressure to Cardiac Output and Systolic Discharge.—Table I and Chart 1 show the relation between the pulse pressure and the cardiac output. The cases have been arranged in the order

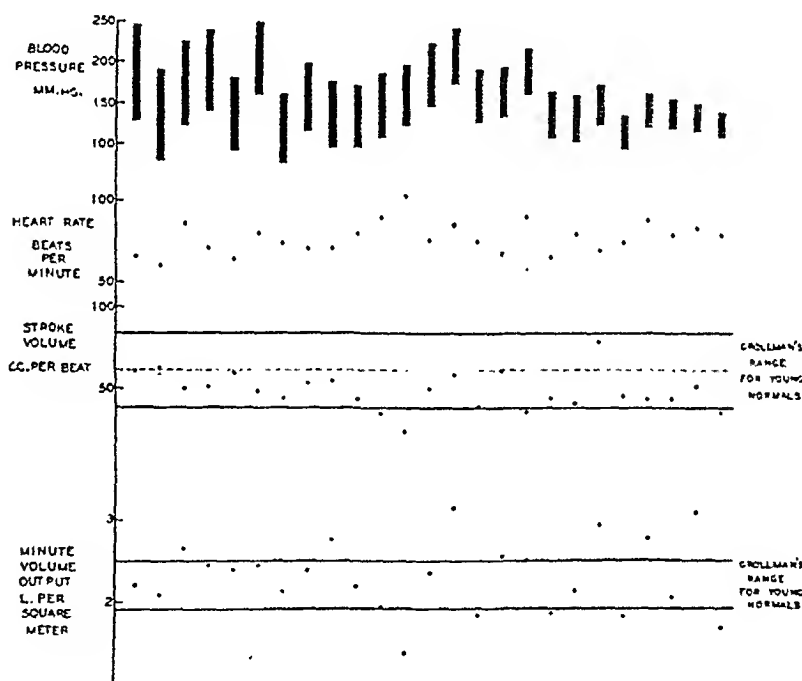


Chart 1.—Relation of cardiac output to pulse pressure in patients with hypertension.

of decreasing pulse pressure. In Chart 1 each vertical column represents one case. The heart rate was normal in all but two of the patients, who had rates of 104 and 92. It may be seen that the stroke and minute output of the heart showed no correlation with the pulse pressure over a range of pulse pressures from 118 to 31 mm. Hg. This is in agreement with observations^{2, 8} of the cardiac output determined by the older method of Field, Bock, Gildea, and Lathrop.⁹ Thus Burwell and Smith,⁵ Weiss and Ellis,² and Grassmann and Herzog¹⁰ found normal cardiac outputs in most cases with arterial hypertension. The stroke volumes of our cases (Chart 1) fell within Grollman's¹¹ range for normal subjects

(38 to 84 c.c. per beat, average 62) in all but four cases, which were slightly low. Our average value, however, was somewhat lower than that obtained by Grollman by the same method. It is of interest that Starr, Doval, Margolies, Shaw, Collins, and Gamble,¹² using an ethyl iodide method, also observed a smaller stroke volume than normal in hypertensive cases. This finding is of significance, for it rules out the theoretical possibility that increased stroke volume is responsible for the elevation of the systolic pressure.

The cardiac output per minute per square meter (Chart 1) showed a wider spread of values than those given by Grollman¹¹ for young normals (2.2 ± 0.3 liters per square meter). Although some of our patients were older than Grollman's, such a comparison is justified since Lewis and Alving¹³ have recently demonstrated that the minute volume output of older age groups remains at the level for adults between twenty and forty years. Of the six cases which varied considerably from Grollman's range, one was an obese woman with a low output (1.36 liters per square meter), whereas four were young persons with high cardiac outputs (2.75 to 3.15 liters). One of the latter may be accounted for by a high basal metabolic rate. In another young patient (fourteen years old) the high value was probably normal for the age of the patient since Starr and his associates¹² have found high outputs for normals below twenty years of age. Thus in only three out of the twenty-five cases studied was the minute cardiac output abnormally high. It should be noted that results may vary as much as 0.4 liter per square meter in the same patient on different days. As in previous studies,² our observations fail to reveal any relationship between the systolic blood pressure and the minute and stroke output of the heart (Chart 2).

The Relation of Pulse Pressure to Circulating Blood Volume, Mean Velocity of the Circulation, and Vital Capacity of the Lungs.—The circulating blood volumes ranged between 50 and 110 c.c. per kilogram and were in most cases normal. The volume has been found to be lower in relation to weight in obese persons and relatively high in emaciated subjects.^{14, 15} The three most extreme values on Table I appear to be high or low for this reason. A few other cases were slightly below the normal of 72 to 100 c.c. per kilogram.¹⁶ The mean velocity of the entire circulation, calculated by dividing the circulating blood volume by the cardiac output per minute, ranged from 46 to 109 seconds (average 78 seconds) and did not vary with either the pulse pressure or the blood pressure. The vital capacity of the lungs was somewhat lowered in a number of the cases. Such a decrease has been observed before and has been shown to result from pulmonary emphysema, which is frequently present in patients with arterial hypertension. No relation existed between the degree of hypertension or the pulse pressure and the reduced vital capacity.

The Size of the Heart.—The standard diameters of the heart and greater vessels have been tabulated and analyzed. It is of interest that in as many as eight cases (32 per cent) the cardiac shadow was within the limits of normal. In the rest of the cases slight or marked enlargement was present. The size of the cardiac shadow could not be correlated with either the height or the duration of the hypertension. Thus in some patients with severe hypertension of two to three years' duration, the cardiac shadow was within normal limits. We have had a similar experience with a group of patients not included in this series. While it is appreciated that a certain type of ventricular hypertrophy (concentric hypertrophy) may be present with normal cardiac x-ray shadow, the findings suggest that a simple correlation between the height and duration of the arterial hypertension and the size of the heart as obtained from x-ray examination does not exist.

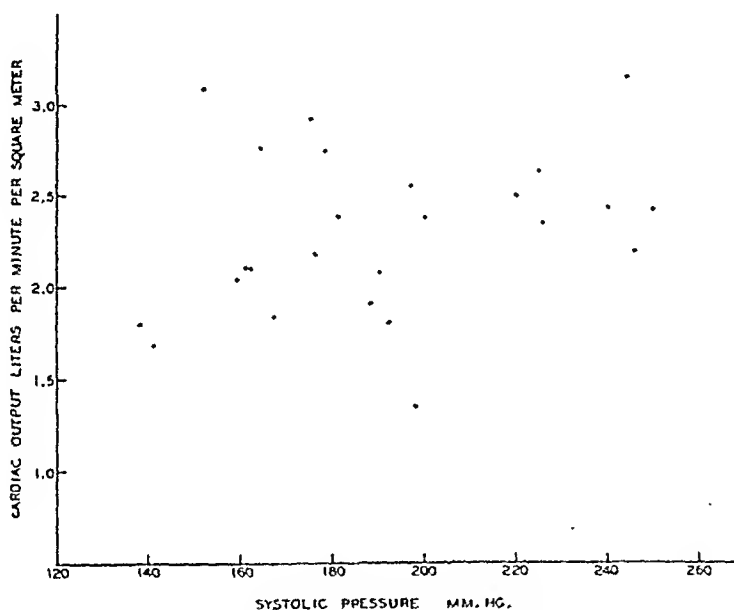


Chart 2.—Relation of cardiac output to systolic blood pressure in patients with hypertension.

The Relation of Pulse Wave Velocity and Oscillometric Measurements to Other Factors Measured.—Table II shows the relationship of pulse pressure to the measurements of arterial elasticity. The change of the pulse wave velocity with the pulse pressure in hypertensive and control patients has been discussed in the preceding paper. In Table II certain of the values there presented have been repeated so that they may be correlated with the cardiac output. In only four cases was there more than slight clinical evidence of arteriosclerosis, and in none of these cases was there marked arterial thickening. It may be seen that the pulse wave velocity bore no relation to the cardiac output. As in the previous work,⁵ the pulse wave velocities were high and the cases with the highest pulse wave velocities, i.e., those with the least extensible arteries, tended to be those with the highest pulse pressures (Chart 3). The effect of

TABLE II

THE RELATION OF THE PULSE PRESSURE TO THE PULSE WAVE VELOCITY IN PATIENTS WITH ARTERIAL HYPERTENSION

CASE	AGE	DEGREE OF ARTERIOSCLEROSIS	ARTERIAL BLOOD PRESSURE			HEART RATE	PULSE WAVE VELOCITY		CARDIAC OUTPUT FROM PULSE WAVE VELOCITY		CARDIAC OUTPUT BY ACETYLENE METHOD		OSCILLOMETRIC MEASUREMENTS			
			SYSTOLIC (MM. HG)	DIASTOLIC (MM. HG)	PULSE PRESSURE (MM. HG)		SUBCLAVIAN- FEMORAL (METERS PER SEC.)	FEMORAL- DORSALIS PEDIS (METERS PER SEC.)	(L. PER SQ. METER)	(C.C. PER BEAT)	(L. PER SQ. METER)	(C.C. PER BEAT)	HEIGHT OF MAX. OSCIL. (MM. HG)	ARM		HEIGHT OF MAX. OSCIL. (MM. HG)
														MOP	MOP	
501	30	+	205	109	99	15.04	15.35	2.50	58	2.38	53	8	140	15	200	
108	29	++	182	91	91	56	11.10	---	4.88	141	2.39	60	17	100	13	100
83	59	++	236	146	90	76	13.84	11.02	3.34	72	2.43	48	---	---	---	---
101	44	++	225	138	87	80	10.94	13.76	2.56	54	2.44	51	17	160	15	180
78	53	+	210	124	86	64	12.74	13.45	3.63	89	1.82	38	12	142	17	165
100	39	+	197	116	81	76	7.36	---	4.15	84	2.64	50	13	115	21	150
13	57	+	157	78	79	72	13.30	14.56	2.60	58	2.18	45	8	90	7	100
107	40	+	234	155	79	72	11.02	---	2.78	66	2.35	50	19	150	21	200
40	44	+	196	120	76	67	10.72	14.86	3.26	80	2.56	62	14	130	16	170
92	32	+	220	150	70	84	11.39*	17.17	2.98	48	2.50	37	---	---	---	---
47	54	+	160	104	56	70	9.33	12.26	2.98	68	2.11	42	10	120	10	130
51	34	+	165	112	53	62	8.20	10.18	2.35	61	1.84	46	7	120	14	150
69	16	+	182	130	52	96	7.61	13.57	3.09	45	3.09	52	6	115	12	120
44	38	+	160	109	51	71	12.14	11.58	2.12	32	2.77	43	12	130	9	175
99	37	+	158	110	48	63	7.36	---	2.66	79	2.93	80	14	130	10	145
106	32	+	136	90	46	70	5.84	---	3.30	89	1.80	47	12	95	12	110
60	33	+	148	112	36	73	---	13.28	1.66	39	2.04	43	---	---	---	---

*Carotid-femoral pulse wave velocity.

changes in the arterial wall itself are difficult to evaluate because of the decrease in distensibility due to the height of the arterial blood pressure.

The oscillometric curves varied considerably in height without reference to the pulse pressure, as has been pointed out in the preceding paper. The point of maximum oscillation (MOP) is somewhat increased above the normal, as might be expected from the height of the blood pressure (Table II). Variation in the height of the oscillations is to be expected from Martin's¹⁷ observations that the oscillations are increased in some hypertensive patients and decreased in others. In cases of essential hypertension he found that the oscillations are often normal or reduced.

The cardiac output calculated from the pulse wave velocity appears in Table II. This calculation has not been found reliable for comparison of different cases. The discrepancy between it and the gaseous determination of the cardiac output is illustrated here.

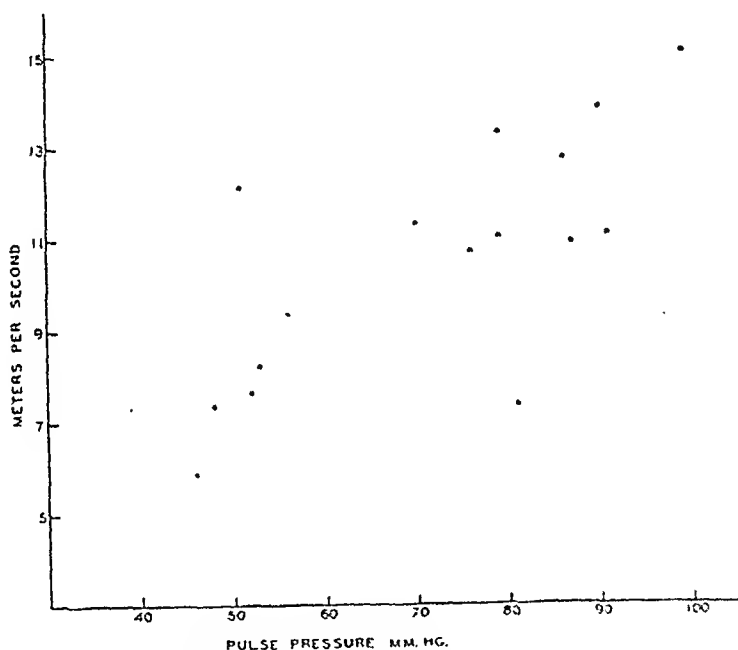


Chart 3.—Relation of subclavian-femoral (aortic) pulse wave velocity to arterial pulse pressure in patients with hypertension.

The Diameter of the Lumen of Radial and Ulnar Arteries in Normal Subjects and in Patients With Arterial Hypertension.—Comparative measurements of the diameter of the radial and ulnar arteries at standard distances from the elbow are presented in Table III. The measurements indicate that no significant variations in the size of the arteries of the forearm can be shown to exist between control subjects with normal blood pressures and patients with a severe degree of arterial hypertension.

DISCUSSION

In 1904 Erlanger and Hooker¹⁸ suggested that the velocity of blood flow could be represented by the product of pulse rate and pulse pres-

TABLE III
DIAMETERS* OF THE LUMINA OF THE RADIAL AND ULNAR ARTERIES IN CONTROL SUBJECTS AND IN PATIENTS WITH HYPERTENSION

STANDARD DISTANCE FROM ELBOW (CM.)	RADIAL ARTERY					ULNAR ARTERY											
	CONTROLS		HYPERTENSIVES			CONTROLS						HYPERTENSIVES					
	1	2	1	2	3	1	2	3	4	5	6	1	2	3	4	5	6
1																	
2																	
3																	
4																	
5																	
6																	
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19																	
20																	
21																	
22																	

*All measurements are the minimum diameters in millimeters as computed from arteriograms.

sure, assuming that the distensibility of the arterial system remains unchanged. By following the changes in pulse pressure in normal persons on standing and after exercise, Rosen and White¹⁹ have brought evidence to show that the pulse pressure is directly proportional to the output per beat in the same individual under conditions that produce essentially the same diastolic pressure and heart rate. In spite of the limitations of applying such reasoning to the present measurements on different individuals, it is of some interest to calculate the product, pulse rate times pulse pressure, in the cases studied because of the wide range of pulse pressures. In the cases listed in Table I this product is about 7,000 to 8,000 in cases with the highest pulse pressures, and about 2,000 to 3,000 in those with the lowest pulse pressures. Over such a wide range as this no essential change in the cardiac output was observed in patients with arterial hypertension. This is in striking contrast with the state of affairs in other pathological states of the circulation, such as thyrotoxicosis, in which Read²⁰ has shown that the pulse rate and the systolic pressure increase with increased metabolism but that the diastolic pressure remains constant so that the pulse pressure increases. Harris²¹ points out that in contrast to Graves' disease an increase in heart rate in tachycardia due to bacterial toxins, in neurasthenia, or in rapid heart action due to amyl nitrite and atropine is accompanied by a small pulse pressure.

In view of the fact that in the series of cases studied the stroke volume, the cardiac output, the mean velocity of the circulation, and hence the mean capillary flow through tissues were normal, and the aortic valves were competent, the marked variation in the pulse pressure-pulse rate index must find its explanation not in cardiac or circulatory factors but in primary changes in the arteriolar and the arterial vascular systems. That the resistance of the arteriolar system is increased in arterial hypertension is generally accepted. Thus Weiss and Ellis^{2, 22} have demonstrated that while the pressure in the skin capillaries is normal, the pressure in the arterioles is considerably increased, at times being more than twice the normal value. In their studies no attempt was made to evaluate the possible rôle of changes in the arteries, in addition to the arteriolar changes. The marked increase in the arteriolar resistance observed should influence primarily the diastolic pressure and to a less extent the systolic pressure. In the types of arterial hypertension associated with a high diastolic pressure and with low, normal, or only moderately elevated pulse pressure, the increased arteriolar resistance can adequately account for the blood pressure levels. This type of arterial pressure is frequently seen in young subjects with acute nephritis. Thus in twenty-five cases with such a diagnosis selected from the records of the Boston City Hospital, the arterial pressure averaged 168/107 mm. Hg.

In the cases in which an unusually high pulse pressure is superimposed on a normal or elevated diastolic pressure, an added factor must be present. We have indicated that theoretically a decrease in either the distensibility or the volume of the arterial system will result in an elevation of the systolic pressure. In the presence of increased arteriolar resistance, such as exists in patients with essential hypertension, relatively less change in arterial elasticity or volume will result in an elevation of the pulse pressure. After due allowance has been made for age and pressure factors, the pulse wave velocity data presented in this and the preceding paper⁵ are interpreted as indicating that a primary loss of elasticity in the wall of the aorta was present in only a few instances in which the systolic pressure was high and the diastolic pressure relatively low. On the other hand, the observations reported also indicate that while the method applied was sensitive enough to demonstrate progressive changes with advancing age, it was not adequate to demonstrate other types of alteration in the tonus and constitution of the larger arteries.⁵ Thus one can only claim that in the majority of patients with arterial hypertension the degenerative changes which normally occur with advancing age are not further accentuated and that such change in the arterial system is not usually the factor responsible for the development of high pulse pressure.

Hochrein²³ has claimed that there is a loss of elasticity in the aortas of patients with hypertension, and he believes that this plays a primary rôle in the elevation of the blood pressure. His conclusion was reached through post-mortem studies of the elastic properties of the aorta; hence there is a possibility that the changes may have been the result rather than the cause of the hypertension. That changes in the arteries alone, however, can lead to an elevation of the systolic pressure is demonstrated in patients with diffuse sclerosis of the aorta and with complete heart-block. In these conditions a high systolic pressure and a normal or decreased diastolic pressure frequently exist. Thus in a study of the hemodynamics of complete heart-block Ellis and Weiss^{24, 25} have observed high systolic pressures in elderly patients, while young patients with an equal increase in the stroke volume exhibited normal pulse pressures. This finding suggests that the normally elastic arterial system possesses a reserve capacity which is able to accommodate even a greatly increased stroke volume with little or no elevation of the systolic pressure. Just as in complete heart-block a markedly increased stroke volume can elevate the systolic pressure in the presence of decreased elasticity of an arterial system, so a priori a normal stroke volume should result in an increase in the systolic pressure if the arterial system is conspicuously narrow. In view of the fact that measurements of the internal diameters of the radial and ulnar arteries have failed to indicate an alteration of the diameters of these vessels, and similarly that the lumina of the arteries of the eyegrounds are usually not narrowed in primary

hypertension, there is basis for the claim that narrowing of the large arteries usually plays no primary rôle in the elevation of the systolic blood pressure.

From the previous discussion it follows that the marked variations in the levels of the systolic and diastolic pressures in hypertension depend on certain types of changes in physical properties of the arterial and arteriolar systems. Extravascular factors, such as cardiac and hemodynamic elements, as a rule do not play a primary etiological rôle in arterial hypertension. The fact that in the majority of patients the elevation of the systolic pressure is relatively greater than that of the diastolic pressure indicates that usually both the arteries and the arterioles are involved in the changes. In various pathological states associated with elevated arterial pressure, however, one or the other of these vessels may be predominantly involved. Thus the character of the blood pressure in patients with acute nephritis and toxemia of pregnancy points to the arteriolar system as the predominant factor. In hypertension associated with the senile type of arteriosclerosis, on the other hand, changes in the arterial system are mainly responsible for the altered circulatory state. It is of particular significance from a point of view of homeostasis that circulatory changes resulting from alterations in the arterial and arteriolar systems are such that the resulting mean flow of the blood through the capillary system remains normal.

The exact nature of the arterial and arteriolar changes in hypertension is not well understood. From what is known at present, however, it is certain that both reversible (functional) and irreversible (organic) processes can take part. With bed rest the systolic and diastolic pressures of patients with severe hypertension frequently return to normal without any change in the efficiency of the circulation. This indicates that, in at least one large group of patients, the alterations in the physical properties of the arterial and arteriolar systems are not permanent, as are the changes with age, but are reversible. Reversible change in the arterial system is also suggested by the work of MacWilliam,²⁶ who has shown that the arteries immediately after death are capable of considerable alteration in tonus, with resulting change in their elastic properties. Evidence recently obtained in this laboratory²⁷ also favors the concept that the hypertonus of the arterioles is also largely reversible and that it may be independent of the vasomotor system.

SUMMARY

1. In order to ascertain the relation of the pulse pressure to the hemodynamics of arterial hypertension, determinations of the cardiac output, blood volume, and pulse wave velocity, and oscillometric measurements have been made in twenty-five cases of hypertension with high, normal and low pulse pressures. In addition, measurements of arteriograms of

the radial and ulnar arteries have been compared in seven control subjects and seven patients with arterial hypertension.

2. The cardiac stroke volume and minute volume output bore no relationship to the pulse pressure in arterial hypertension. In spite of the high pulse pressure, the heart rate, stroke volume, minute volume output of the heart, and the blood volume were found to be essentially normal. The pulse wave velocity was high, and it bore a certain relation to the pulse pressure. The lumina of the radial and ulnar arteries were of the same width as in the control subjects.

3. The results of the investigation are interpreted as indicating that the high systolic pressure of hypertension depends in part on alterations in the physical state of the aorta and arteries. As judged from the clinical behavior of the blood pressure, the nature of the change within the arterial wall is not uniform. In the group studied the change was of a different nature from that found as a result of aging processes.

4. There are changes in the physical properties of both the arterial and arteriolar systems in arterial hypertension. The relative degree of involvement of the arteries and arterioles can vary considerably in various types of arterial hypertension. The exact nature of the changes in the arterial and arteriolar systems is not known.

5. In arterial hypertension there is a remarkable homeostatic adaptation of the heart and of the circulation to the primary changes in arterial and arteriolar systems.

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SOME CASES OF SLOW PULSE ASSOCIATED
WITH ELECTROCARDIOGRAPHIC CHANGES IN CARDIAC
PATIENTS AFTER MAXIMAL WORK ON THE
KROGH ERGOMETER

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IN WORKING out a cardiac functional test with Krogh's bicycle ergometer we encountered some peculiar pulse curves which will presumably be of interest to the clinician who tries to estimate the functional capacity of the heart by examination of the pulse during or after exercise. The remarkable feature of these pulse curves is that immediately after maximal work on the ergometer the pulse rate falls off temporarily to a point considerably below the resting value. This transitory phenomenon is accompanied by transitory massive changes in the electrocardiogram. As we have observed this pulse phenomenon only in connection with unquestionable pathological working electrocardiograms, we are inclined to attribute some pathological significance to its appearance.

Before mentioning these curves we shall outline briefly the technic we have employed. The patients are examined fasting, after a suitable rest on a couch in the laboratory. The resting pulse rate (base line) is determined electrocardiographically after the patient has been sitting relaxed on the bicycle for five minutes. The work is performed on the Krogh bicycle ergometer, with a riding tempo constant by metronome (30 rotations per minute), and with increasing load, three minutes' work with each load, the change of load taking place *during* the ride. With some experience this change of load is easily made in a few seconds. After reaching the maximal amount of work the patient is instructed to place his feet on the footboards of the bicycle and sit perfectly relaxed. The pulse rate is measured electrocardiographically every three minutes during the work, in such a way that the counting of the pulse is always made in the same fraction of the minute, making all the counts directly comparable. In the afterperiod the pulse is counted every minute until it is found to remain constant for four consecutive minutes. The pulse count is made with a transportable Boulitte electrocardiograph. The muscular unrest during the work is moderated by the insertion of a small condensator in the chest lead. Orientating experiments have shown that the results obtained with such a continually increasing load during the work give the same information as do single tests in which the patient rides the bicycle with one load at a time and

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with a period of complete rest after each test; this technic saves a good deal of time. This method gives a pulse value for each amount of work besides information about the course of the pulse curve for about ten minutes after the work. Each patient is submitted to the ergometer test at least three times (on three consecutive days).

The present studies have given us the impression that the working pulse as it appears with a given amount of work is a value that can easily be reproduced from day to day under the given experimental conditions. In the not particularly frequent instances in which a distinct training effect could be made out, the experiments were prolonged until it was practicable to obtain conformable results allowing of graphical smoothing.

The working electrocardiograms are taken (by Kaj Larsen) with an amplifier apparatus furnished by Siemens-Halske, constructed by Professor Warburg, and tried out by Warburg and Larsen.¹ As it was

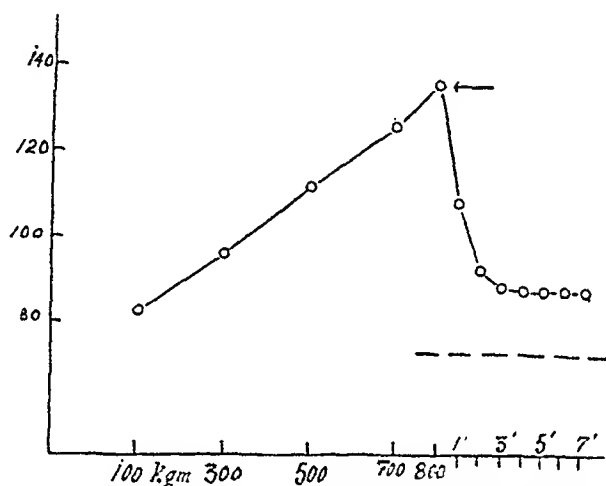


Fig. 1.—Horizontal turn of pulse curve after work in normal persons.

----- Resting pulse
 o— Pulse
 — End of work

found impracticable with the patient sitting on the ergometer to obtain the state of muscular rest required for good electrocardiography with *extremity* leads, we have instead employed leads from the wall of the chest, as suggested by Groedel,² partly from the xiphoid process, partly from the left axilla at a level with and a little lateral to the apex of the heart. The electrodes were small metal-felt-saline electrodes, fixed with a rubber band. In the following, for practical reasons the lead from the xiphoid process will be designated as Lead *d* (dexter), and the lead from the left axilla as Lead *s* (sinister). But whether the two leads, as Groedel thinks, represent the potential changes in the right and left ventricles, respectively, is a question we shall leave open for the present. In order to eliminate the factor of uncertainty that might result from a limited knowledge of electrocardiograms from the thoracic leads, in one series of tests we have placed the patient in an easy-chair alongside

the ergometer before and after the work and then have taken in immediate succession electrocardiograms from the ordinary leads and from thoracic leads.

As is well known, the pulse curve falls at once when the work is discontinued. As a rule, however, this fall of the pulse rate goes on only for a few minutes, when the curve makes an abrupt turn to a horizontal level and becomes steady somewhat above the level of the resting pulse. This turn of the pulse curve is very pronounced and easy to recognize (Fig. 1).

With a view to the findings and comments in the following we wish here to emphasize explicitly that in normal persons we have never seen the pulse curve fall below the level of the resting pulse (base line) in the period of about ten minutes we employ for observation. After this period the curve falls off but exceedingly slowly, and it may take several hours before it reaches the base line. For practical reasons, we have taken no interest at all in this part of the pulse curve; as already mentioned, we have ceased counting the pulse as soon as we have obtained constant readings for four minutes in succession.

Also the comparatively few controls we have examined show a rather uniform appearance of thoracic electrocardiograms before and after work (Fig. 2). As we are interested here particularly in the behavior of the S-T interval and T-wave, it will be appropriate to describe these features briefly. During rest both S-T_d and S-T_s are most often a little above the isoelectric line, and both T-waves are distinctly positive. Immediately after the work the S-T intervals are seen to approach or reach the isoelectric line, without going below this level. Immediately after work the T-waves may be a little higher, of the same height, or a little lower than before work, but they increase in every case during the first minute of work, reaching a maximum in one to two minutes; after this they decrease, in most cases reaching in four to six minutes a lower level than before the work, and then they slowly increase toward their original height. In no case in normal persons were the T-waves isoelectric, much less negative.

Up to the present we have examined 50 patients in the Departments A, B, and P of the Rigshospital, including 25 normal (i.e., as far as the heart is concerned) and 25 cardiac patients (mostly cases of myocardial degeneration). The material is gathered in order to obtain average values for the pulse frequency in normal persons and patients during work, but it is yet all too small to allow of any comprehensive account of the results. The cases presented in this paper, however, are so characteristic, we think, that it is reasonable to give a preliminary account of them now, regardless of the possible frequency of their occurrence.

CASE 1.—C. C., male, fifty-eight years old. Past history was negative as to rheumatic fever, diphtheria, and scarlet fever. Ten years ago he had an attack of mumps associated with orchitis. For the last seven months the patient had com-

plained of pain of an oppressive character in the chest, localized to the manubrium and provoked by rapid movements and heavy meals but not by exposure to cold. The pains were radiating, at first to the left arm, then to the right arm and to the back, also down in the legs. The pains were not accompanied by anxiety or dyspnea and subsided after rest. There was typical "second wind" and often attacks of profuse sweating. There had never been any dyspnea, palpitation of the heart, or edema. The patient had worried a great deal during the past year.

Physical Examination.—The patient appeared healthy, but a little obese. Heart: Ictus in the fifth intercostal space, within the midclavicular line; the sounds were

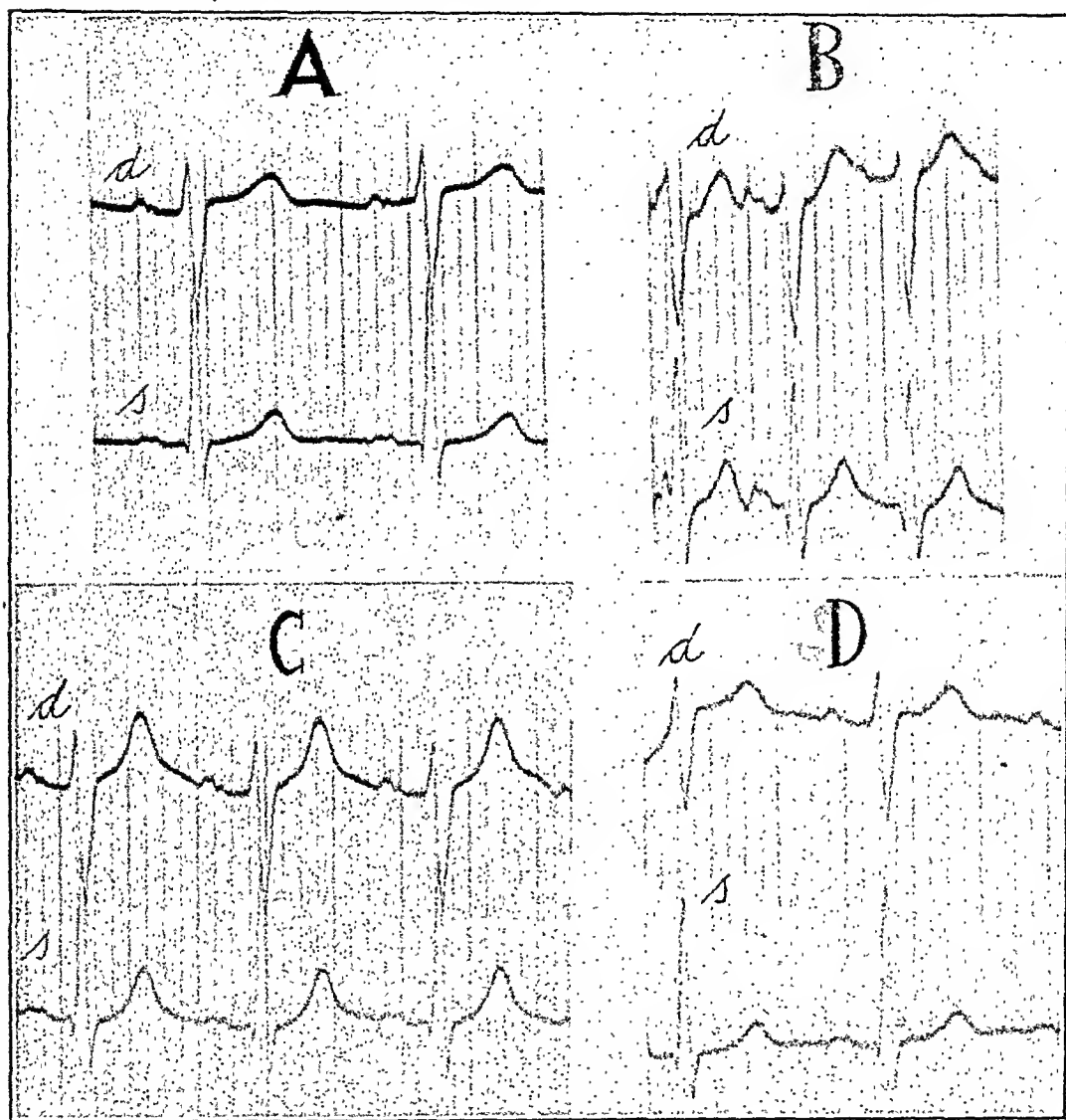


Fig. 2.—Working electrocardiograms of normal persons: A, thoracic lead before work; B, 10 seconds after cessation of work; C, 2 minutes after cessation of work; D, 6 minutes after work. (Time marker, 0.05 second; 1 millivolt—20 mm.)

clear, $A_2 > P_2$; the second sound was weak over the aorta as well as over the pulmonary artery. No demonstrable stasis in the lungs, liver, or legs.

Special Examinations.—Wassermann and Kahn reactions were negative. Hemoglobin content was 106 per cent; sedimentation test (one hour), 7 mm. The urine showed no abnormalities. Blood pressure readings were 140/90, 145/85, 142/80. Vital capacity, 4.7 liters. Roentgenography: Heart measured $15 \times 32 \times 8$ cm., no definite abnormalities. Abdomen: Rather large hiatus hernia. Electrocardiography: Left preponderance. Registration of heart sounds: No abnormalities.

Summary of Positive Findings.—Dilatation of the aorta, preponderance of the left side of the heart, diaphragmatic hernia.

Diagnosis.—Angina pectoris, aortic dilatation, hypertrophy of the left ventricle, and diaphragmatic hernia.

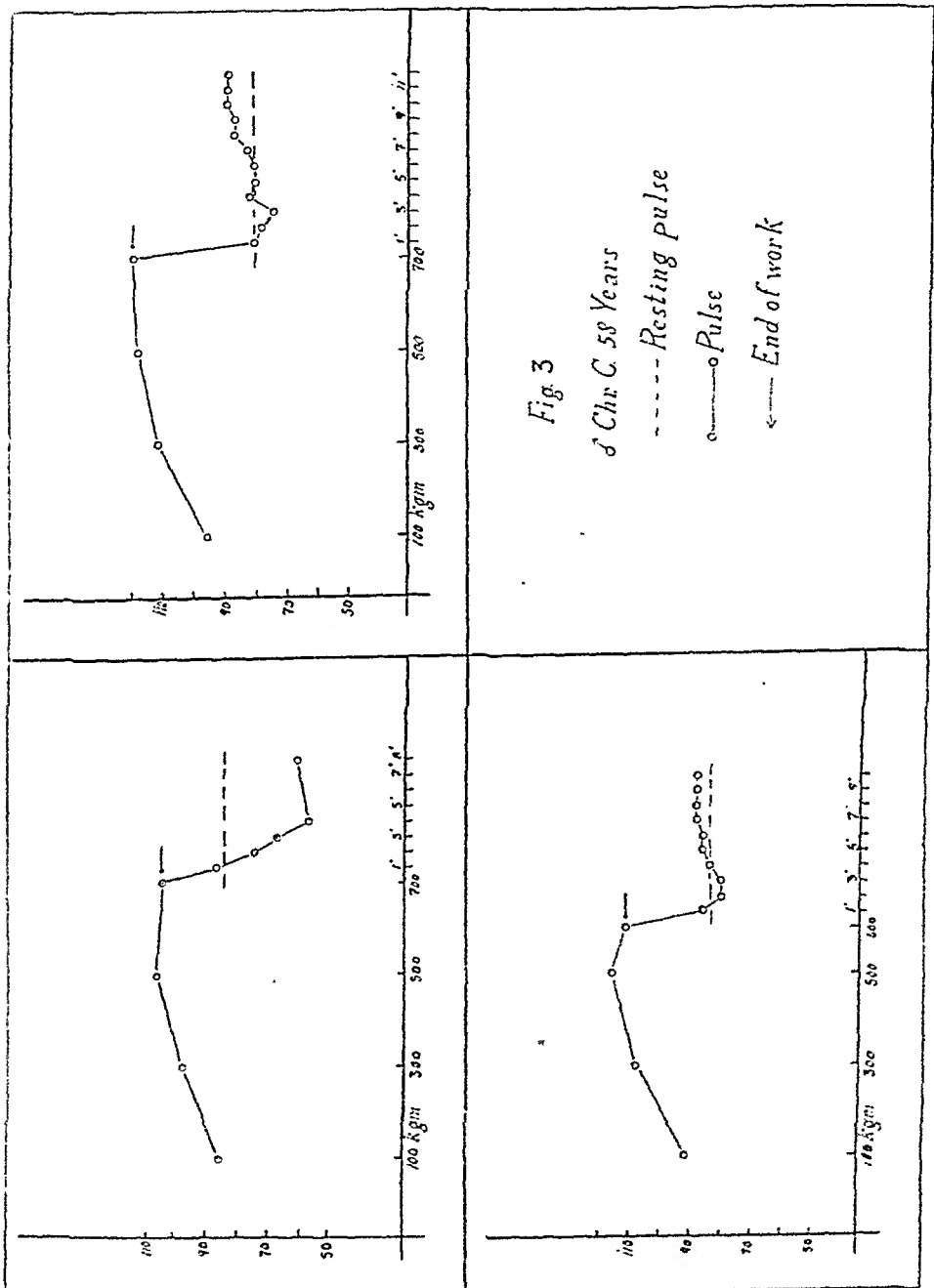


Fig. 3.—Ergometer tests on May 14, 16, and 18.

Ergometer Test (Fig. 3).—The maximal output of work was 700 kilogram-meters per minute. Even with an output of 600 kg-m the patient began to have pain back of the manubrium. After cessation of work the pulse curve falls off in three minutes to a minimum at a vary-

ing distance below the base line; then it rises slowly. The patient was very exhausted after the first test which had to be discontinued on that account.

Working Electrocardiograms, (Fig. 4).—Four ergometer tests showed pronounced electrocardiographic changes, consisting in a pronounced depression of S-T_s and inversion of T_s. In one experiment, in which the patient rode 100-300-500-600 kg-m and in which electrocardiograms were taken during the bicycling, the electrocardiographic changes were found to begin at 500 kg-m and to be very pronounced at 600 kg-m. At 500 kg-m the patient began to have pain in the chest, and at the same time the pulse rate ceased rising (500 kg-m. with a pulse rate of 119, 600

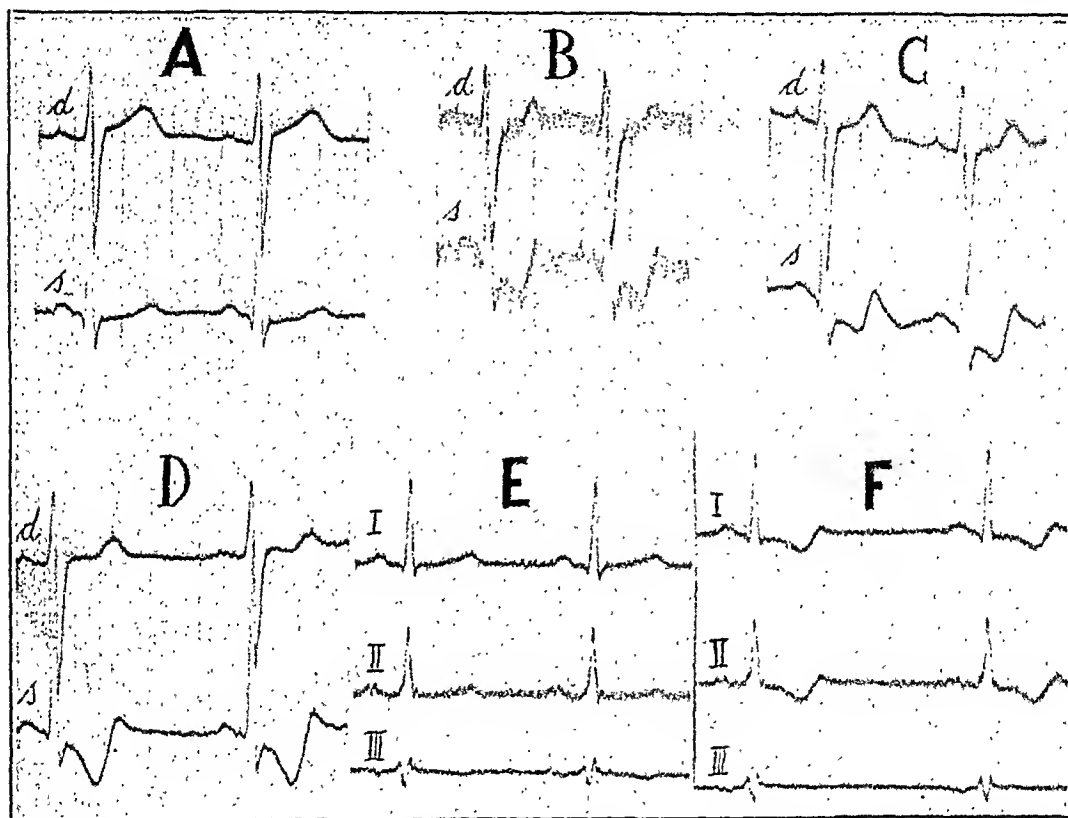


Fig. 4.—C. C. Working electrocardiogram: A, thoracic lead before work; B, during bicycling with a load of 600 kg-m; C, 5 seconds after cessation of work; D, 2 minutes after cessation of work; E, extremity lead before work; F, extremity lead 2 minutes after work. (Time marker, 0.05 second; 1 millivolt—20 mm.).

kg-m. with a pulse rate of 120). The depression of S-T_s was greatest immediately after the cessation of work, and then it diminished gradually. The inversion of T_s, on the other hand, kept getting more pronounced and reached its maximum in from one and one-half to three minutes; then it subsided. Still, it took nine minutes after cessation of work before the electrocardiogram looked fairly like the prework record. In Lead *d* the changes were only slight. S-T_d prior to the work was seen to be somewhat above the isoelectric line; immediately after cessation of work this interval was seen to have become isoelectric, and T_d was seen at the same time to have been lowered a little bit. These

changes had disappeared six minutes later, and nine and twelve minutes after work T_d was somewhat higher than before work. In Fig. 4 E and F the changes here described in the thoracic lead correspond to a considerable depression of $S-T_1$ and $S-T_2$ and to the inversion of T_1 and T_2 . According to our present experiments, the absence of electrocardiographic changes in Lead III is quite in keeping with the fact that in the thoracic lead the changes are pronounced only in Lead s .

CASE 2.—J. P. N., male, fifty-two years old. Past history was negative as to rheumatic fever, diphtheria, and scarlet fever. The patient claimed he had always been well until December 2, 1933, when suddenly while working he had an attack of severe pain back of the sternum, radiating out into both arms and around to the back, and being accompanied by marked dyspnea, anxiety, and sweating. The attack lasted between one and two hours. He had to quit work and go home, where his doctor gave him morphine, which relieved him. He was then hospitalized for two months. He has since had frequent attacks of constricting precordial pains, radiating in various directions (at present to the right ear only) and, in the beginning, accompanied by dyspnea and anxiety. The attacks have diminished in intensity, but they are elicited very easily by walking or by plentiful meals, and sometimes they appear also during rest. The attacks last, as a rule, from five to ten minutes and subside when the patient stands still.

Physical Examination.—There was slight obesity and, on admission, congestion of the face, with a cyanotic hue. There was no resting dyspnea, no jaundice. Auscultation of the heart revealed normal findings. There was no demonstrable congestion of the lungs or liver. A suggestion of edema was noted about the ankles.

Special Examinations.—Wassermann and Kahn reactions were negative. Blood pressure readings were 175/105, 160/95, 155/95. Sedimentation test (one hour), 42 mm., hemoglobin, 98 per cent. The urine showed no abnormalities. Roentgenography: Heart measured 15×31 cm.; the shape was suggestive of dilatation of the left half of the heart. No dilatation of the aorta (7 cm.). Electrocardiography: Left preponderance; low T_1 , isoelectric T_2 . Vital capacity, 3.9 liters. Registration of heart sounds: No abnormalities.

Summary of Positive Findings.—Cyanosis, edema about the ankles, roentgenologically demonstrable changes in the size and shape of the heart, preponderance of the left side of the heart, low T_1 , and isoelectric T_2 .

Diagnosis.—Coronary sclerosis, sequelae of coronary thrombosis.

Ergometer Test (Fig. 5).—As in Case 1, the pulse curve is distinctly negative, i.e., within a few minutes after cessation of work the pulse curve falls off to a point below the base line, and then it rises again. Also this patient complained of anginoid pain at the end of the work.

Working Electrocardiograms (Fig. 6).—Four ergometer tests show pronounced changes after the work characterized by depression of both $S-T$ intervals and by a transitory total inversion of both T -waves. After nine to ten minutes the electrocardiogram appears normal once more.

CASE 3.—R. H., male, fifty years old, had an attack of myopathy in the right pectoralis region two years ago. Otherwise the patient gave a past history of good health. During the last year he had been troubled with attacks of retrosternal pain radiating out to the left arm. More recently these attacks increased in intensity and frequency, making their appearance in the night during rest as well as in the day during work. They were not associated with any particular anxiety, and

the pain appeared never to reach the intensity which is most common in attacks of anginoid pain. Apart from this, the patient had never shown any sign of organic heart lesion. Lately, he had many attacks every day. The pains yielded readily to nitroglycerin.

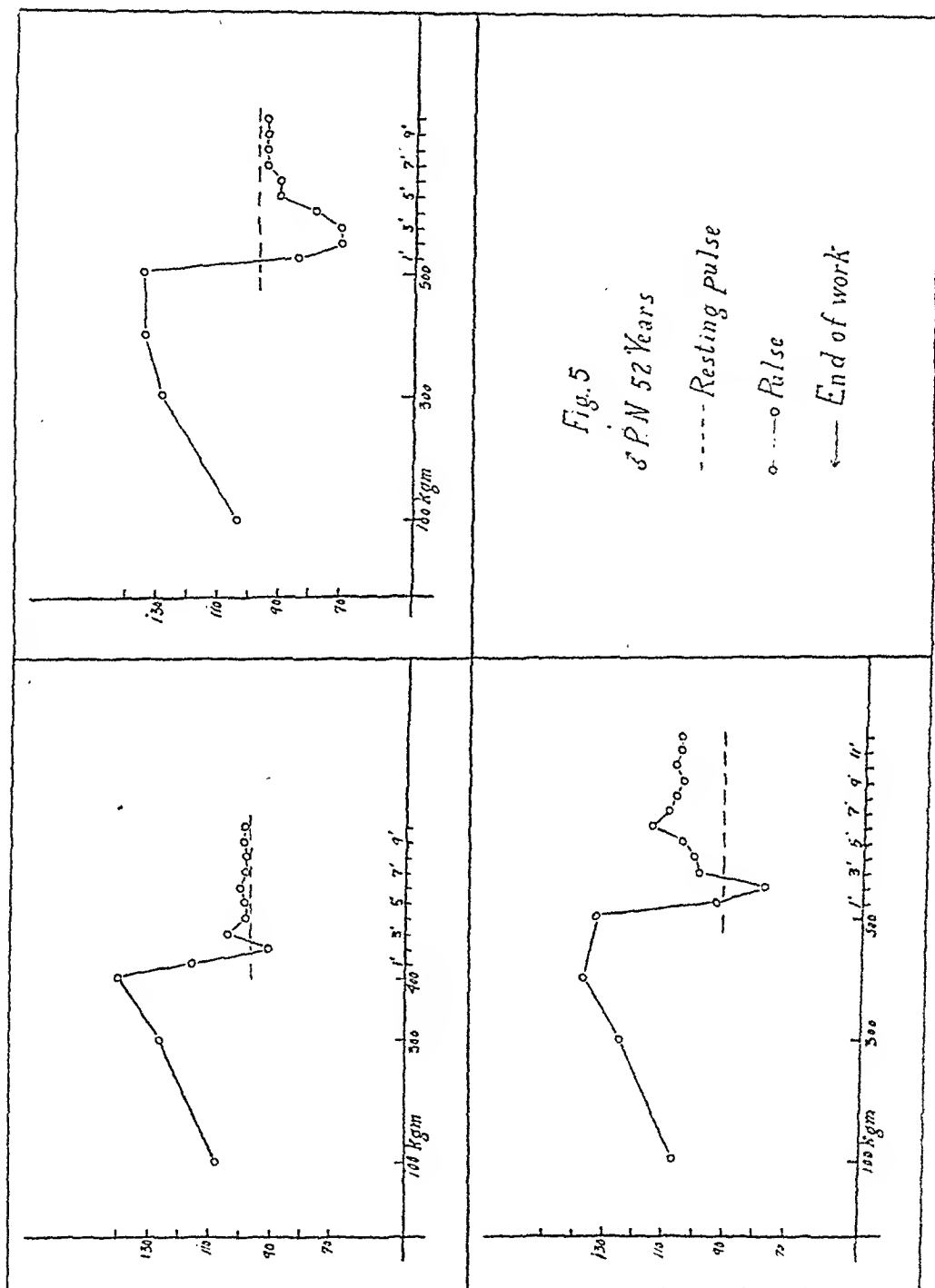


Fig. 5.—Ergometer tests on April 24, 25, and 26.

Physical Examination.—Slight obesity. On percussion the lung borders are found to be at ribs 7, 9, and 11. The breath sounds are vesicular, without abnormal sounds. Auscultation of the heart: Heart lung-covered; heart sounds faint, clear; action regular. No demonstrable congestion of the lungs, liver or legs. No demonstrable myopathic processes in the pectoralis.

Special Examinations.—Wassermann and Kahn tests were negative. Sedimentation test (one hour), 4 mm.; blood pressure readings were 130/60, 130/70, 120/70;

hemoglobin, 89 per cent. The urine showed no abnormalities. Roentgenography of the heart: Normal form and size (hardly 15 cm. against 29.5). No increase in the width of the shadow of the vessels. No sign of aortic arteriosclerosis. Moderate arteriosclerosis in the right leg and forearm. Electrocardiography: Q_2 is greater than 25 per cent of the greatest wave present. Registration of heart sounds: No abnormalities.

Summary of Positive Findings.—Emphysema, large Q_2 , and peripheral arteriosclerosis.

Diagnosis.—Emphysema of the lungs (slight degree), observation for myocardial degeneration, angina pectoris, arteriosclerosis.

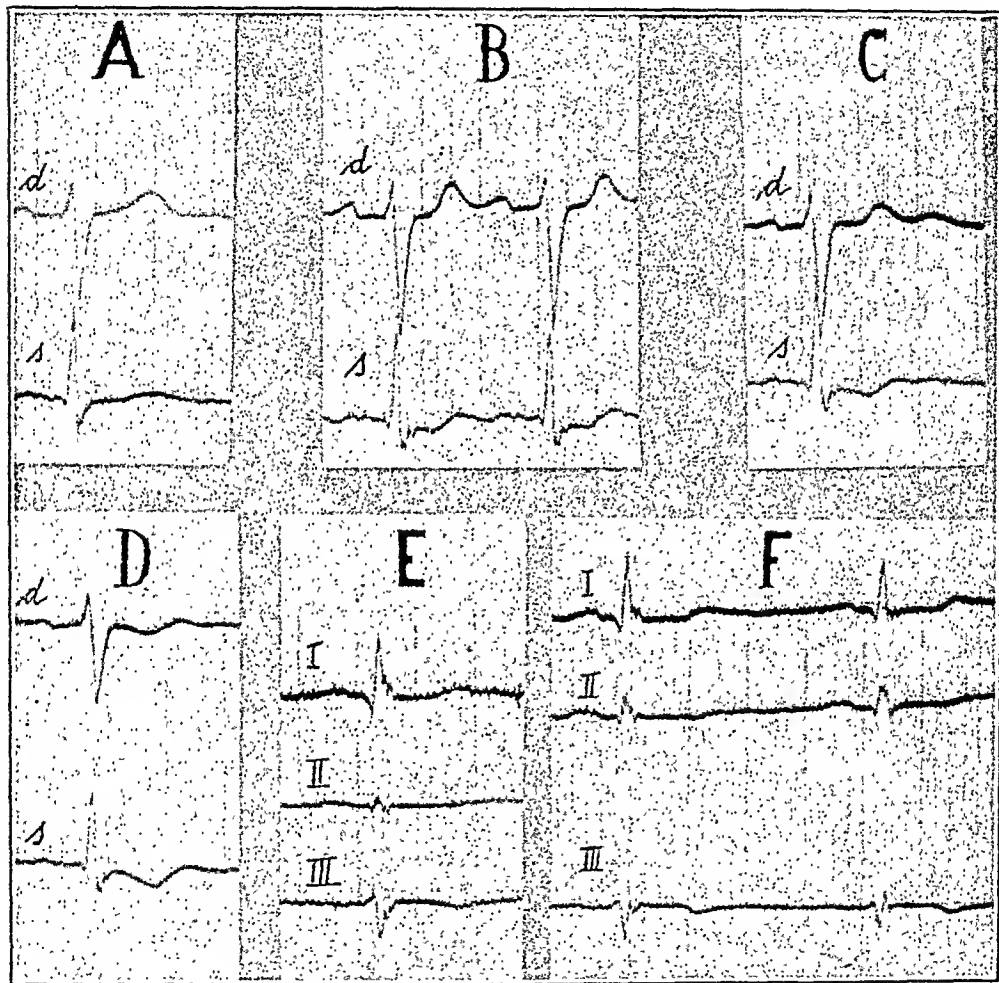


Fig. 6.—J. P. N. Working electrocardiogram: A, thoracic lead before work; B, 30 seconds after cessation of work; C, 1 minute after cessation of work; D, 2 1/2 minutes after cessation of work; E, extremity lead before work; F, extremity lead 2 minutes after work. (Time marker, 0.05 second; 1 millivolt—20 mm.)

Ergometer Test (Fig. 7).—The maximal output of work was 500 kg-m per minute. The working capacity was limited by precordial pain. All three tests show a negative pulse curve shortly after the cessation of work.

Working Electrocardiogram (Fig. 8).—Ergometer tests on three different days show uniform electrocardiographic changes. Cessation of

work is followed immediately by a marked depression of the S-T interval in both thoracic leads. Both intervals take an almost horizontal course and turn into T-waves which are still distinctly positive immediately after the cessation of work; then the T-waves become diphasic

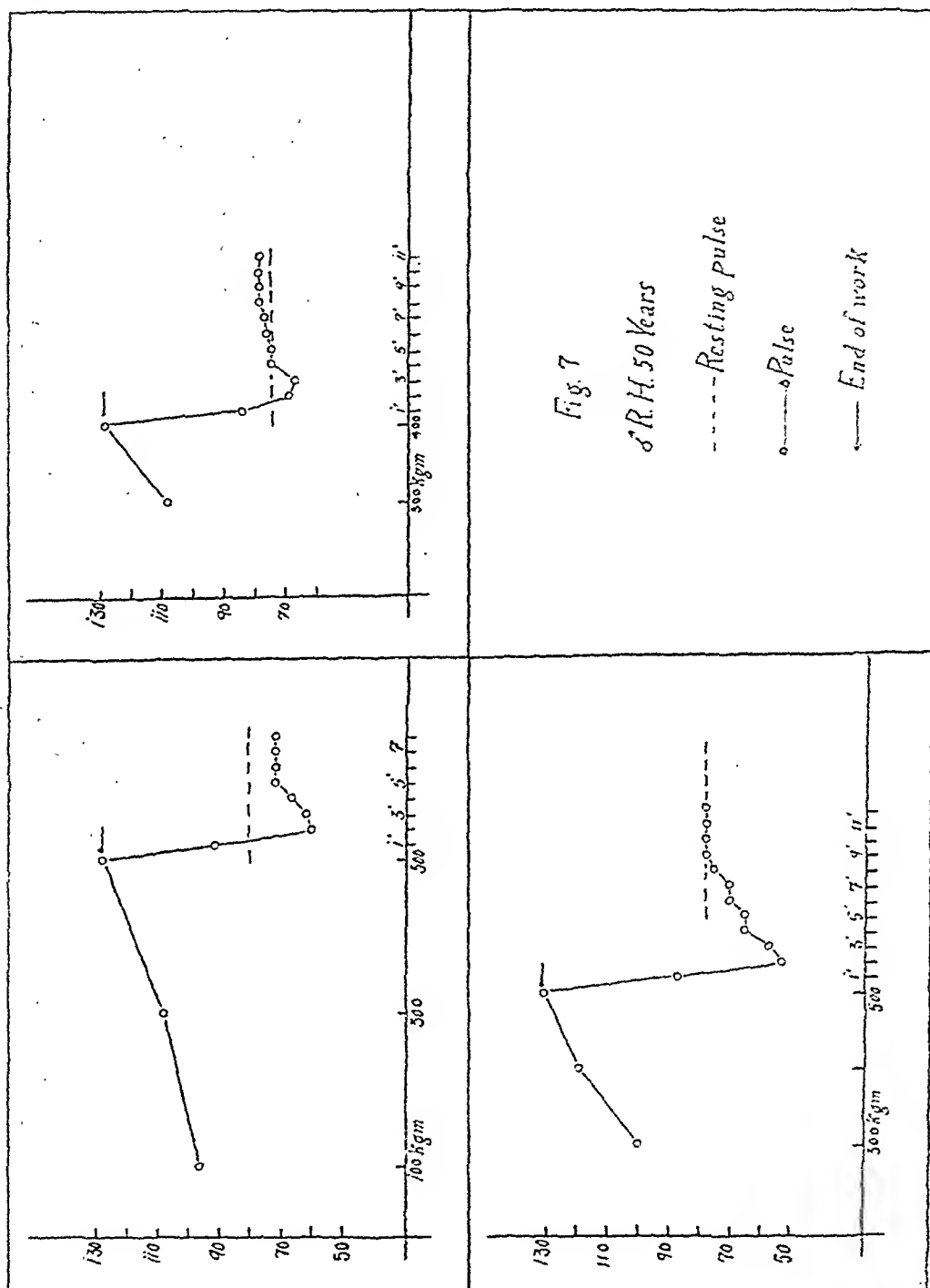


Fig. 7.—Ergometer tests on April 12, 13, and 15.

with a steadily increasing negative part and a steadily decreasing positive part. About two minutes after the cessation of work the S-T intervals are considerably less depressed, and now they are followed by great, entirely negative T-waves. These changes soon begin to regress, however, and the T-waves become entirely positive once more, after go-

ing through the diphasic stage. But it took nine minutes after the cessation of work before the electrocardiogram had the same appearance as prior to the work. In this case then the electrocardiogram in nine minutes goes through the same phases it otherwise takes some weeks or months to go through, after an acute attack of coronary thrombosis. On comparison with records *E* and *F* (Fig. 8) the corresponding changes

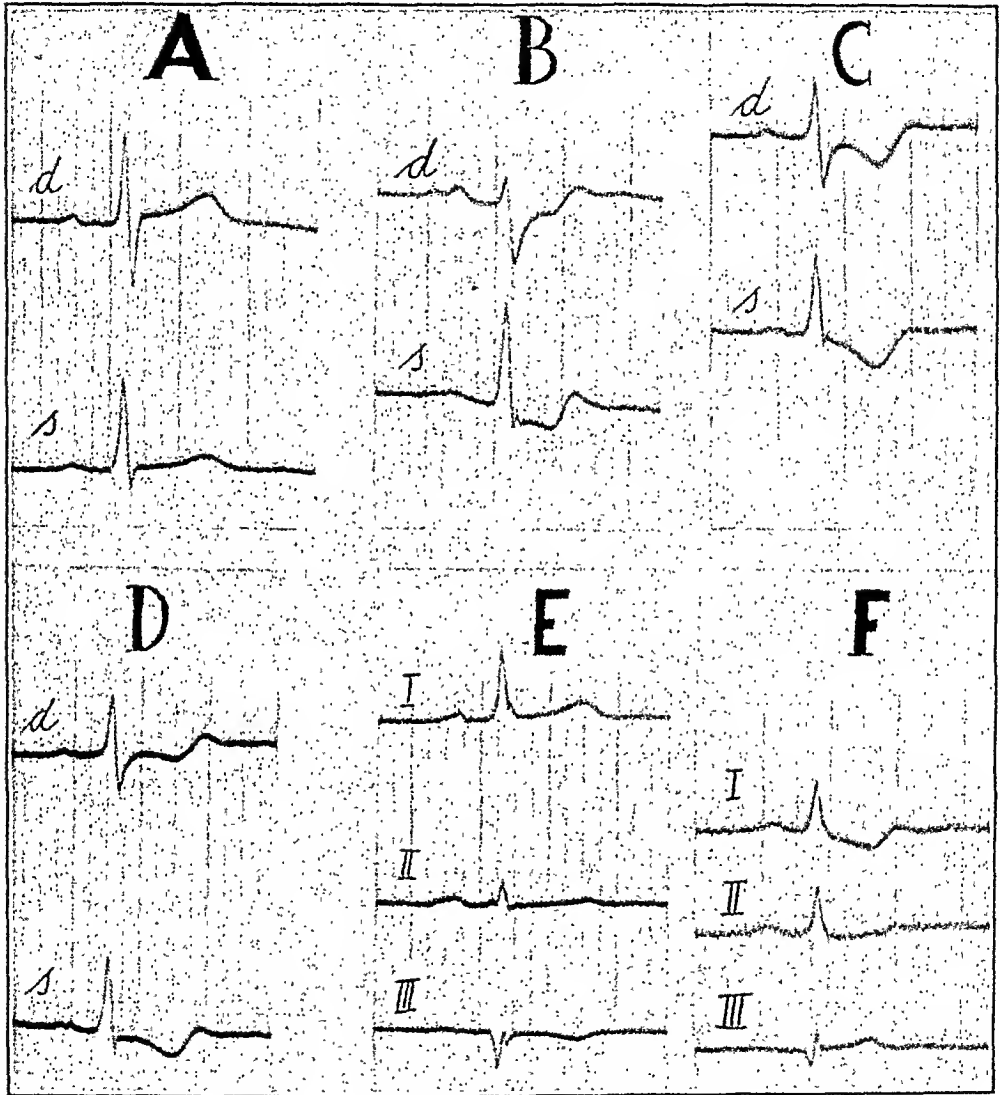


Fig. 8.—R. H. Working electrocardiogram: *A*, thoracic lead before work; *B*, 15 seconds after cessation of work; *C*, 2 minutes after work; *D*, 5 minutes after work; *E*, extremity lead before work; *F*, extremity lead 1½ minutes after work. (Time marker, 0.05 second; 1 millivolt—20 mm.)

in extremity leads are seen to be: Depression of $S-T_1$ and $S-T_2$ and elevation of $S-T_3$. T_1 is positive before the work; after work it is negative, or diphasic with a preponderance of the negative part. T_2 remains unchanged, low positive; T_3 changes from negative to positive. These changes also regress in about nine minutes after cessation of work.

CASE 4.—H. G., male, fifty-three years old, had scarlet fever in childhood; otherwise he gave a past history of good health. During the last half year before admission to hospital the patient had been troubled a little, while working, with dyspnea without palpitation of the heart or edema. During the month preceding examination he had had a sensation of precordial oppression, and rapid walking had

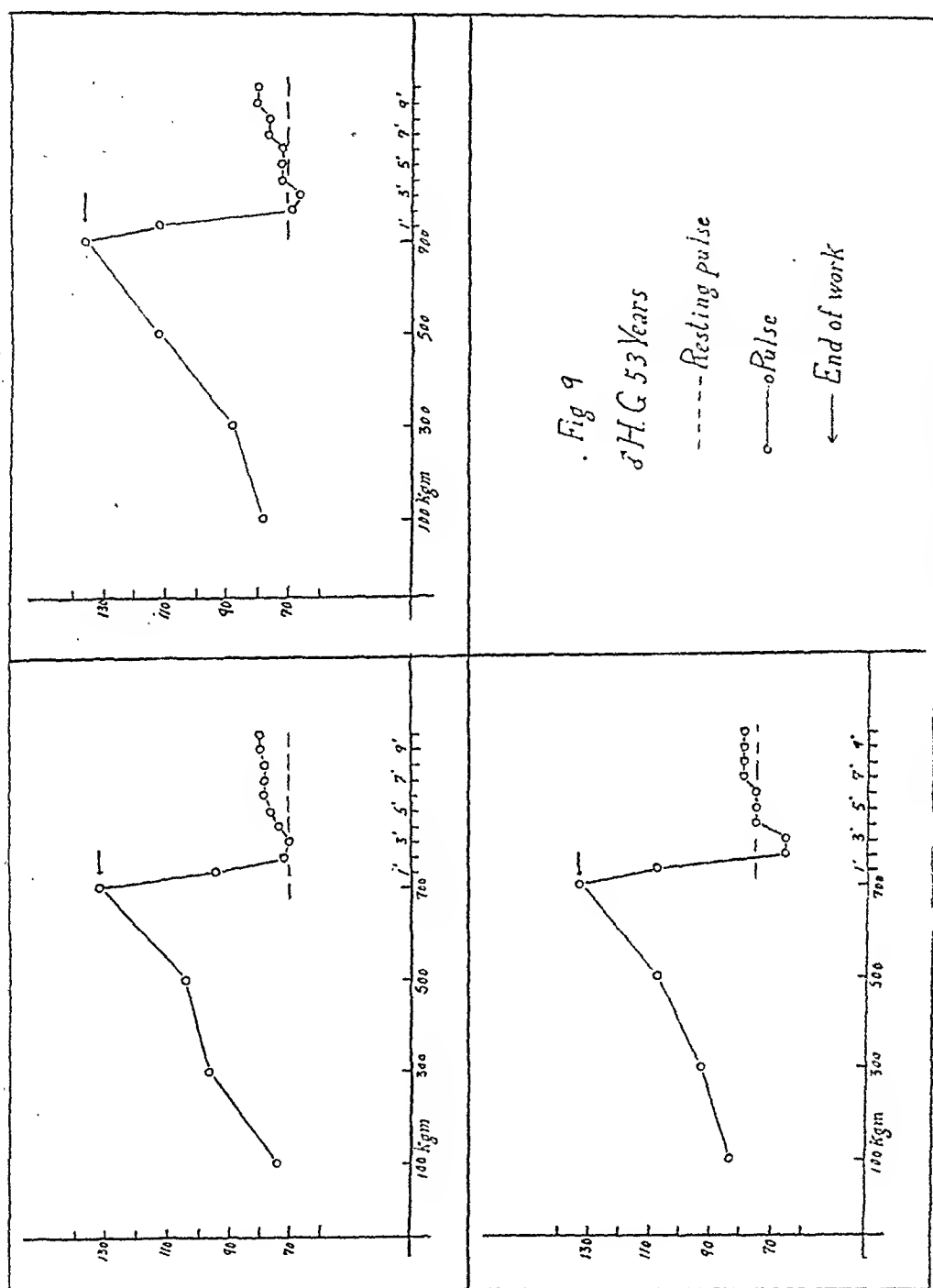


Fig. 9.—Ergometer tests on June 8, 11, and 12.

been followed by pain on the lateral surface of both arms. Once the pain appeared in the night. There was no pain in connection with meals or changes in temperature. The patient was a heavy smoker.

Physical Examination.—Nutrition was fair. There was no dyspnea or cyanosis at rest. Auscultation: The heart was partly lung-covered; the impulse of the apex beat was made out indistinctly in the fifth intercostal space, 1 cm. inside the

papillary line. The sounds were faint but clear; $A_2 > P_2$. No stasis was demonstrable in the lungs, liver, or legs. No myopathic processes were demonstrable in the muscles of the chest.

Special Examinations.—Wassermann and Kahn tests were negative. Sedimentation test (one hour), 2 mm.; blood pressure, 130/80; hemoglobin content, 112 per cent. The urine showed no abnormalities. Roentgenography of the heart: Dilatation of the left ventricle (demonstrable in the second oblique diameter); diffuse

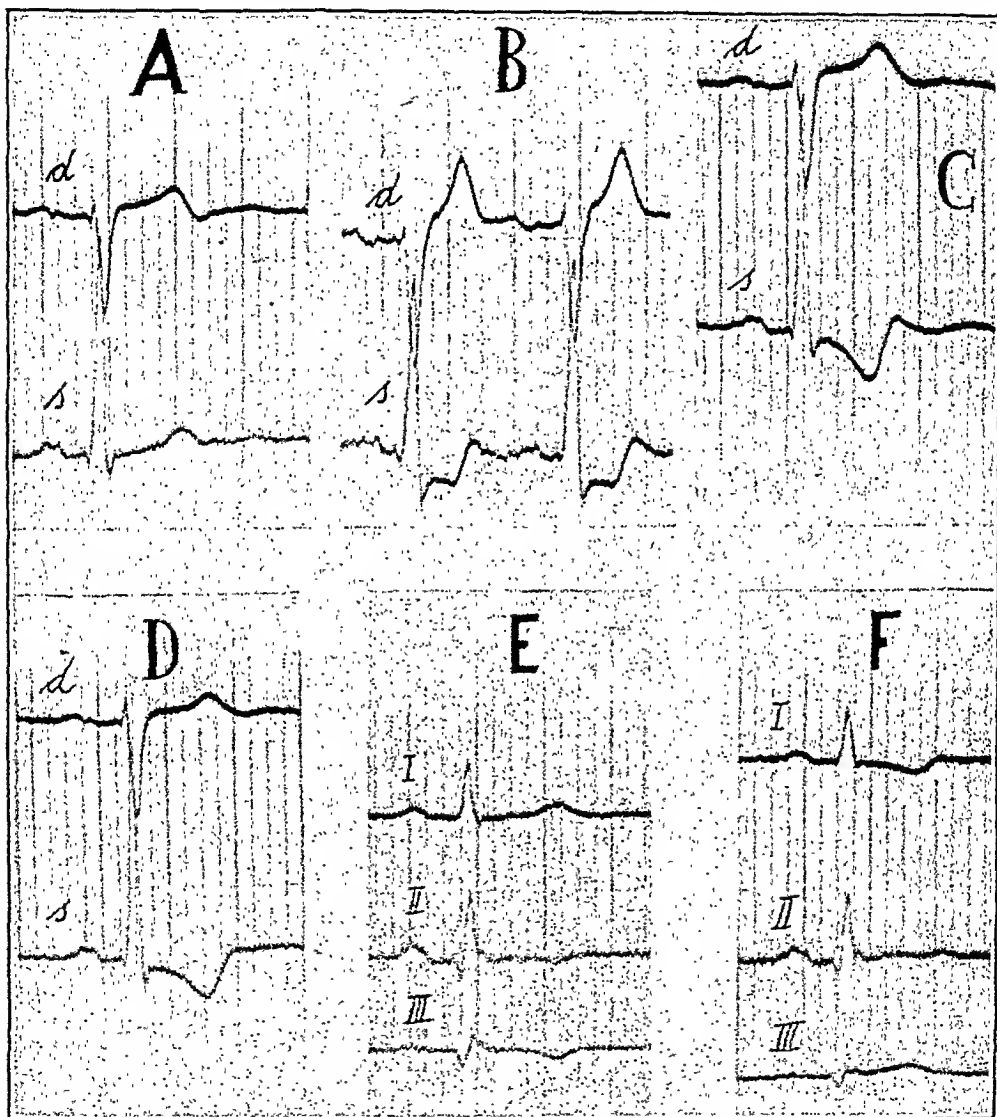


Fig. 10.—H. G. Working electrocardiogram: A, thoracic lead before work; B, 20 seconds after work; C, $4\frac{1}{2}$ minutes after work; D, 6 minutes after work; E, extremity lead 5 minutes after work; F, extremity lead 5 minutes after work. (Time marker, 0.05 second; 1 millivolt—20 mm.)

dilatation of the aorta (8.5 cm.). Roentgenography: lungs, no abnormalities; peripheral arteries, distinct arteriosclerosis. Registration of heart sounds: No abnormalities. Electrocardiography: Isoelectric or very low T_2 .

Summary of Positive Findings.—Accentuation of A_2 , roentgenologically demonstrable dilatation of the left ventricle and aorta, peripheral arteriosclerosis.

Diagnosis.—Dilatation of the aorta, hypertrophy of the left ventricle, arteriosclerosis, coronary sclerosis (?).

Ergometer Test and Working Electrocardiogram (Figs. 9 and 10).—The records show similar changes, of about the same duration, as in the preceding cases.

DISCUSSION

These four patients, then, are men about fifty years old who complain of more or less typical anginoid pain during work. Two of these cases (Cases 2 and 4) represent probably a fully established condition of coronary sclerosis; in the other two cases the evidence of some organic heart lesion (in particular, coronary sclerosis) is more uncertain. At any rate, one would hesitate very much to designate these two patients as disabled (the Danish Act of Invalidity Insurance requires a decrease of the working capacity to less than one-third in order to designate an applicant as disabled). In these cases the ergometer test proves to be a valuable supplementary examination, as the above mentioned working tests can hardly leave any doubt about these patients' being quite unfit for manual work.

As mentioned, we have never encountered the negative pulse curve in normal persons, and we have seen it only in a certain number of cardiac patients. As far as our experience goes, the occurrence of this type of pulse curve is decidedly of pathological significance, but nothing definite is known about the cause of this peculiar phenomenon. With a view to the accompanying electrocardiographic changes, the idea suggests itself that this phenomenon involves a relative anoxemia of the myocardium, but this idea is contradicted by the fact that anoxemia experiments as a rule give an increase of the pulse rate even in the presence of pronounced electrocardiographic changes. If, nevertheless, one would maintain the possibility of this idea, one would have to imagine at any rate that the myocardial anoxemia which is produced during work is more pronounced than the myocardial anoxemia resulting from inspiration of oxygen-deficient air. There is another possibility: namely, that it may be a question of a central phenomenon. One might imagine, for example, that bradycardia of central origin produces an inadequate coronary circulation and, with this, the electrocardiographic changes. This theory is contradicted by the fact that the patients present no other cerebral symptoms; moreover, in one of the cases here reported (Case 3) an anoxemia test gave cerebral anoxemia with convulsions, loss of consciousness, and a slow pulse without electrocardiographic changes. Finally, we cannot refute the possibility that the bradycardia and the electrocardiographic changes may be two independent phenomena, coinciding merely by chance so that, for instance, the bradycardia may be due to sclerosis of the cerebral arteries, while the electrocardiographic changes result from sclerosis of the coronary arteries. In that case, however, one would expect on examination of arteriosclerotic patients now and then to find the negative pulse curve as an isolated phenomenon

without electrocardiographic changes, but we have never so far observed such a phenomenon in our working tests. For the sake of completeness, it is to be mentioned that blood sugar determinations have shown that the peculiar course of this pulse curve is not due to a decrease in the blood sugar concentration.

In our ordinary functional tests for estimation of working men's disability and similar conditions we have been accustomed to look upon the rapid pulse after work as a criterion of heart disease. To us it seems interesting, therefore, to learn that there are cardiac affections that manifest themselves only by a slow pulse after work.

SUMMARY

A report is made of four patients with clinical evidences of heart disease who, after work with Krogh's bicycle ergometer, presented the unusual feature of a prompt drop in the pulse rate to a rate below the resting level and at the same time showed transient gross changes in the electrocardiogram.

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ACROCYANOSIS: A STUDY OF THE CIRCULATORY FAULT*

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AN INSTANCE of acrocyanosis was first adequately described by Cassirer¹ in 1900 under the name of "acrocyanosis asphyxia chronica." Nothnagel,² as early as 1866, mentioned a patient who, to judge from a rather inexact description, may have been a sufferer from this disorder. Although regarded as rare by the earlier authors, we find the condition mentioned frequently in present medical literature, and there can be little doubt that at least in mild form it is a widespread malady. With the development of modern methods for the study of peripheral circulatory phenomena, it is surprising that, with the exception of Lewis' and Landis' recent contribution,³ which will be discussed later, little exact knowledge as to the vascular mechanism has been elucidated.

Our interest in acrocyanosis was aroused by its presence in a patient having bilateral cervical ribs.

CASE REPORT

A married white woman, twenty-nine years old, complained of having had cold, blue, moist hands since childhood. She had always lived in a temperate climate and had never suffered from frost-bite or chilblains. Otherwise the past history was irrelevant with the possible exception of bimonthly attacks of migraine for years. The blueness of the hands and the sweating of the palms were worse during the winter months, when the hands were immersed in cold water, or when she was emotionally disturbed. For five years she had noticed inconstant pain, numbness, and tingling in the region of the radial aspect of the left elbow.

She was a slightly built, alert individual with a low blood pressure and a rather rapid resting pulse rate. Physical examination was noninformative except for the appearance of the hands. The fingers were long and tapering, and the skin was soft and pliable. With the hands dependent, blueness of the skin, most pronounced over the dorsal surface of the knuckles, could be traced upward to where it stopped abruptly shortly above the level of the styloid process. The palmar surfaces were likewise cyanotic, especially in the creases. Swelling was never present. The radial and ulnar pulses were equally vigorous, and they did not fade when the arms were elevated above the shoulders. No sensory changes of the forearms or hands were demonstrable.

A roentgen ray study of the neck disclosed bilateral, short, thick, cervical ribs. The left rib down to its vertebral attachment was surgically removed, with immediate relief of the unpleasant sensations about the left elbow.

The patient has been studied over the period of a year since this procedure.

The operation has been without effect on the circulatory disturbance of the hands, according to observations during this time. The behavior of the left hand in reference to the experimental procedures later to be described has been identical

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with that of the right. We believe it improbable that the cervical ribs have contributed toward the circulatory disturbance in this patient's hands because: (1) it is extremely unlikely that irritation of vasomotor nerves from rib pressure could have persisted unchanged since childhood without eventually causing degeneration of those fibers and resultant symptoms of vasomotor palsy; (2) removal of the rib left the malady uninfluenced; (3) as succeeding evidence will show, a local vascular defect exists which is not strictly dependent upon the innervation of the vessels involved.

In addition to this patient, a milder degree of acrocyanosis has been encountered in two healthy young men who have kindly lent themselves for study.

METHODS OF STUDY

Charts of skin color were prepared after the method of Thomas Lewis.⁴ Three color scales of nine shades each were made and numbered as follows: scale 1, from the color of bloodless skin to that of skin engorged with arterial blood, *A*, *1B*, *1C*, *1D*, *1E*, *1F*, *1G*, *1H*, and *1*; scale 2, likewise from the cream color of bloodless skin to the color of skin engorged with purely venous blood, *A*, *2B*, *2C*, *2D*, *2E*, *2F*,

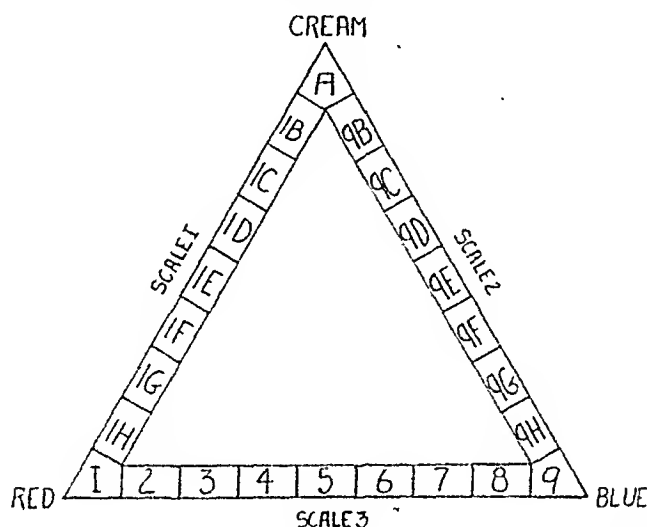


Fig. 1.—Arrangement of color scales in the shape of a triangle.

2G, *2H*, and *2*; scale 3 from the color of skin engorged with arterial blood through admixtures of increments of venous blood to the tint of blood in which all the hemoglobin has been reduced. Since these colors cannot accurately be reproduced, the scales may be arranged for the purpose of better visualization into an equilateral triangle as in Fig. 1. We have found these scales, although difficult to make, of great usefulness in confirming and recording objectively observations which otherwise are extremely liable to errors of subjective interpretation.

Measurements of peripheral pulse volume were made by the finger plethysmograph described by Scapham and Johnson.⁵ Our instrument consists of a glass tube approximately the size of a finger. One end of the tube is closed by a rubber diaphragm with a hole in the center. From the other end, rubber tubing of small diameter is led off to the shaft of a 1.0 c.c. pipette containing a bubble of alcohol. The finger is inserted through the diaphragm into the glass tube, and the oscillations of the bubble, synchronous with the rise and fall of the finger volume with each pulse beat, are photographed on a moving film. To facilitate the comparison of data obtained by this instrument, we have devised a method of expression termed for convenience, "volume flow ratio." The distance between and the height of the waves are each measured directly in millimeters from the photographic tracings.

The former is divided into the latter, giving the ratio. If either the height of the wave increases (numerator) or the distance between the waves decreases (denominator), the ratio will increase, or in other words, will indicate an increment of total blood flow through the finger. Conversely, decrease in the ratio indicates lessening of the total blood flow. With the conditions remaining constant (i.e., length and bore of the tubing, distance of bubble from film, etc.), the changes in volume flow ratio may be compared under differing experimental conditions.

The greater part of this study was conducted in a room where temperature could be controlled to within 1°C . and relative humidity to within 10 per cent. Unless otherwise stated, skin temperature readings were taken from the pads of the fingers using a Leeds and Northrup galvanometer.

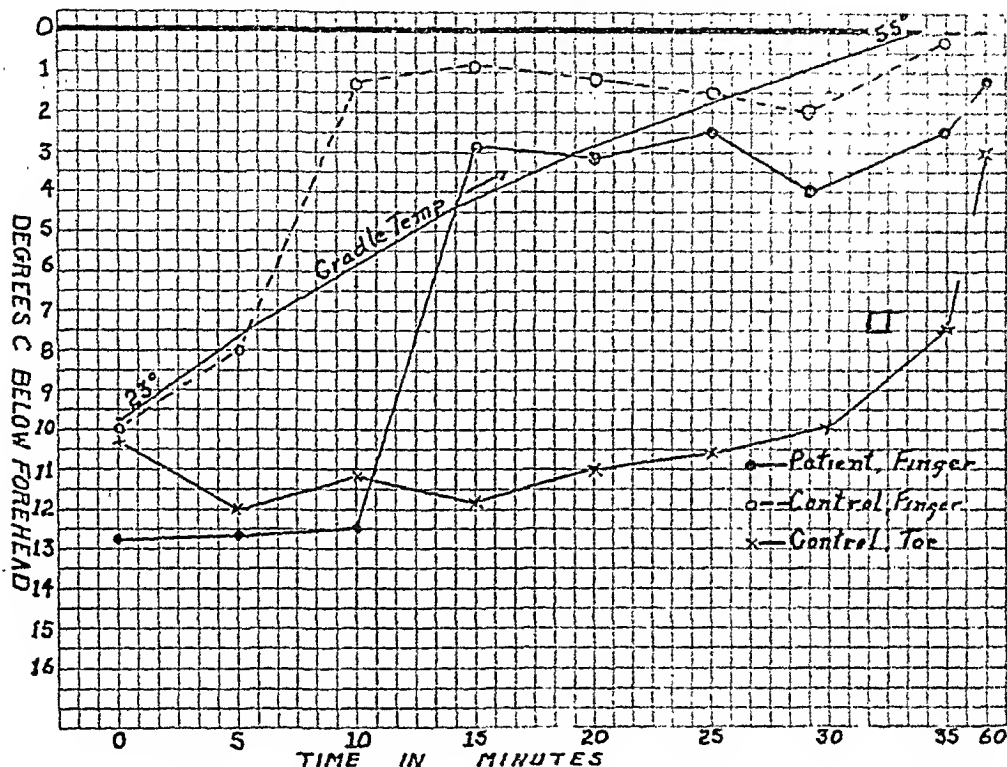


Fig. 2.—Vasodilatation in the digits resulting from application of heat to the trunk.

RESULTS

Response to Procedures Which Produce Maximum Vasodilatation.—After skin temperatures reached equilibrium with a room temperature of 24°C ., the patient, clad only in a sheet, was placed in a wire cradle covered with blankets and heated by carbon filament lamps. The hands to the wrists and the head were exposed, and skin temperatures of the fingers and of a point above the bridge of the nose were read at five-minute intervals. Temperatures of the mouth and cabinet were likewise followed. Results are expressed graphically in Fig. 2. Temperature of the finger tips approximated that of the forehead in fifteen minutes, and capillary pulsation of the finger pads was noted at the twelfth minute. This response was checked by the method of Maddock and Coller,⁶ in which the body is wrapped in blankets for one hour, and by immersion of two extremities in hot water during which the rise in skin tempera-

ture of the diseased limbs is followed, as described by Landis and Gibbon.⁷ In all experiments the digital arteries widened quickly, equally, and fully as measured by the increase in skin temperature and in digital pulse volume. This response precludes the existence of structural arterial disease. The rapid and equal flushing of the fingers during reactive hyperemia after Lewis' method⁸ was further evidence in this direction.

Response of the Hand Vessels to Varying Environmental Temperatures.—The spontaneous temperature and the color of this patient's fingers were observed almost daily during the summer and fall. The

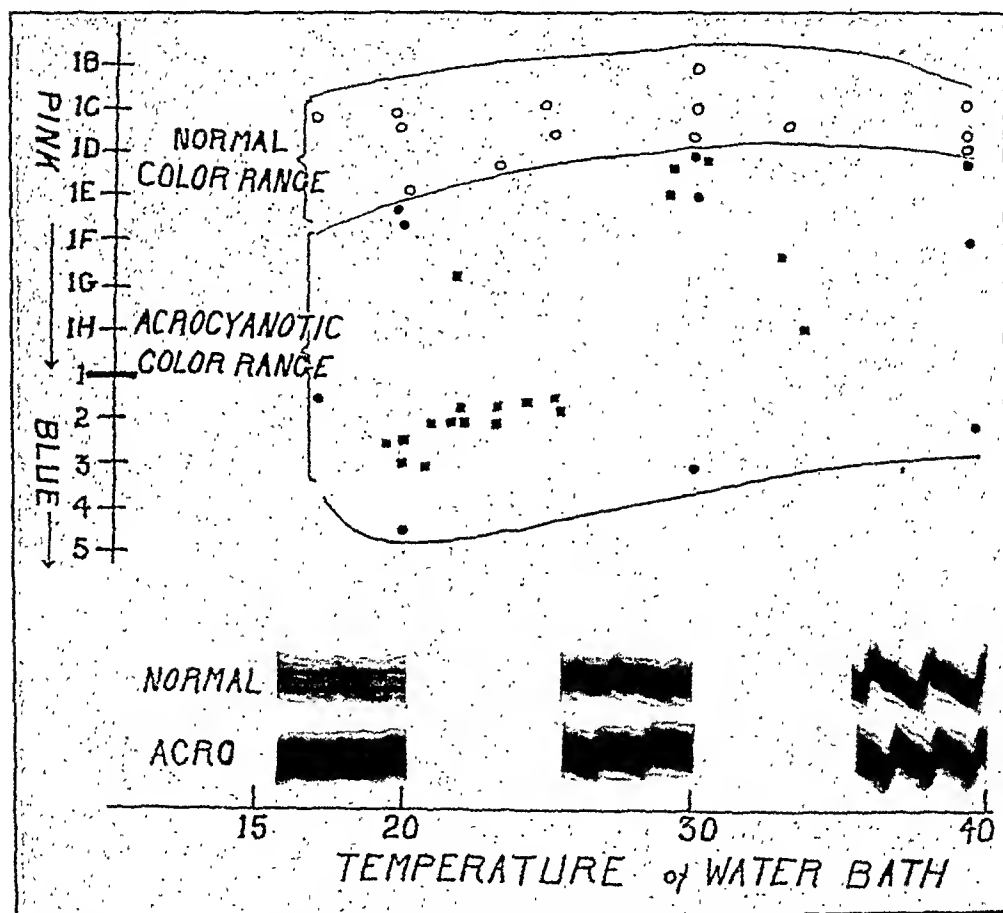


Fig. 3.—Color range and digital pulse volume of fingers at varying spontaneous and experimentally induced skin temperatures.

temperature of the room in which these observations were made varied from 15 to 30° C. during this period. An entirely normal color of the hands was never observed. At room temperatures below 24° C. there was uniformly a cyanotic tinge (color 2 to 4) and at higher temperatures cyanosis was often observed. If absent, it was replaced by an increase in pinkness not encountered in the skin of normal individuals in such an environment. Elevation of the hands above the head in the latter circumstances produced blanching to a normal depth of color. Temperature of the fingers was uniformly from 1 to 5° below that of the surround-

ing air. To test this matter under more carefully controlled conditions, the hands of this and of two other patients, together with those of normal individuals, were submerged in water baths at 15, 20, 30 and 40° C. for periods of ten minutes, and the effects upon the color of the skin and the digital pulse volume were studied. The range of observed color changes is given in Fig. 3. The circles represent colors after immersion in water and the squares, those occurring spontaneously at similar skin temperatures. A sample of the pulse tracings is also given. It will be observed that there is little overlap between the color range of normal and acrocyanotic hands under the conditions imposed. In the individuals tested we failed to confirm Lewis' statement² that the hands of normal

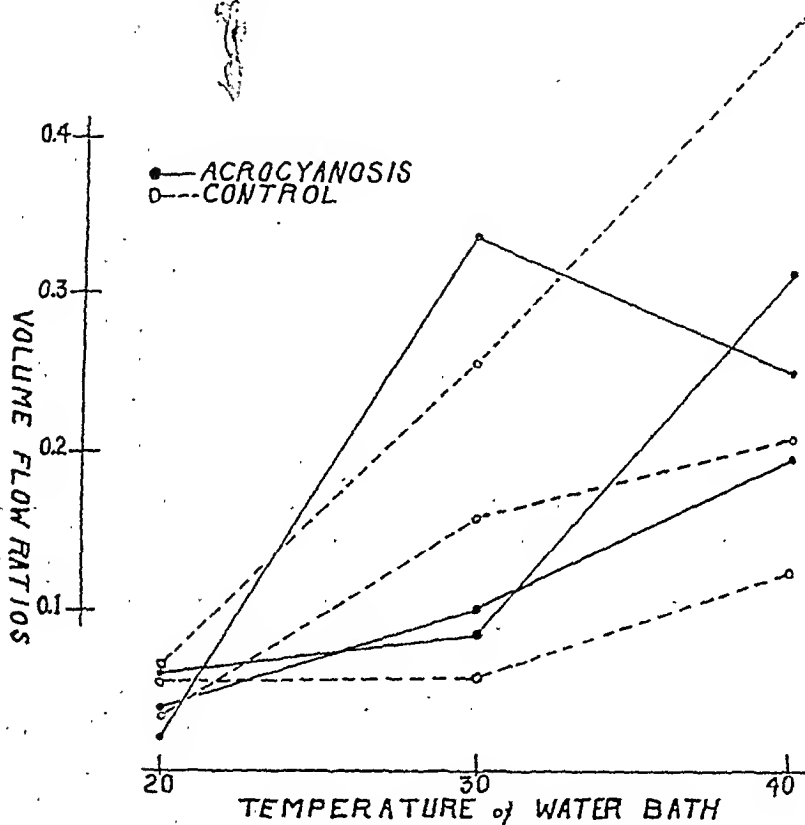


Fig. 4.—Relative increase in blood flow through the fingers produced by increase in external temperature.

persons may turn blue when subjected to a water temperature of 20° C., but this may be due to differences in room temperature, clothing, etc., prevailing in the two groups of experiments.

The changes in volume flow ratios of the fingers under these experimental conditions are charted in Fig. 4. Whereas possibly the ratios of the patients with acrocyanosis were slightly lower on the average than the normal after the immersion at 20° C., the normal increment in flow ratios with the subsequent increases in water-bath temperatures is evident. While the curves of increase of blood flow through the fingers are not as smooth as those published by Lewis and Landis,³ this difference may be due to the method of measurement employed by us. We feel that these results are essentially in accord with those of these

writers. Their statement that the digital arteries in acrocyanosis respond in a normal manner to increments in local external temperature is justified.

An Evaluation of the Venous and Capillary Blood Flow.—The earlier writers, particularly Erben,¹⁰ believed that in acrocyanosis there was an obstruction to the venous return because of increased tonus of the subcutaneous veins. He found that the subcutaneous venous network is poorly filled when the arm is experimentally congested, whereas the intracutaneous veins are overfilled and atonic. He postulated a "dissociation" in tonus between the intracutaneous and subcutaneous venous networks. Lewis has disproved the conception of venous obstruction by relatively simple observations which we have easily confirmed in the following manner: Our patient's hands, at a uniform temperature and tint of blueness (color *I*), were placed on a table at a level 8 inches below the heart. One hand was then elevated above the head for intervals of one, two, five, and ten seconds, respectively, after which it was quickly lowered to the table and the color immediately matched on the color scales. After one second's elevation, the hand was less blue (color *2*); after two seconds, pink (color *1F*); and after five and ten seconds' elevation a deeper pink was observed (color *1G* to *1H*). In other words, on elevation of the hands the blood quickly drained away from the capillaries and collecting venules. When the hand was lowered, these vessels rapidly refilled. Lewis and Landis² offer further evidence that there is no venous obstruction by observations of capillary pressure during and following closure of the arm veins by a pneumatic cuff. The capillary pressure, after having reached a point equal to the pressure imposed upon the veins, immediately returned to the precongestion level upon deflation of the cuff.

In this connection two other observations are worthy of note. 1. With the hands of our patient at heart level, light pressure upon the skin produced an area of blanching which did not return to its previous color until six seconds had elapsed, whereas a normal skin, subjected to the same procedure, returned to its former color after three seconds. The significance of this observation will be commented upon later. 2. With the patient's hands below heart level, an entirely normal depth of skin color was never observed, regardless of the temperature of the skin. If the fingers were pink, however, elevation of the hands above the head would, as previously mentioned, result in paling to a normal appearance. We believe that this phenomenon is due to the fact that at all times the minute vessels of this patient's skin are dilated. The depth of color therefore is a passive result of the amount of blood circulating in them, the degree of filling being dependent upon the arterial inflow and the venous drainage, factors obviously related to the position of the hands relative to the heart.

Many observers^{11, 12, 13} have commented upon the dilatation of the capillaries, particularly of the venous side of the loop, as rather charac-

teristic of the microscopic appearance of the nail bed in acrocyanosis. This was strikingly evident in our patient regardless of the temperature and color of the skin at the time of observation. There is no need to recapitulate the details of the microscopic morphology as we cannot add to the descriptions of other workers.

The refractoriness of the minute skin vessels of the patient was further evidenced by a study of the response to adrenalin and nitroglycerin, as follows: After the patient, her trunk and legs covered by a woolen blanket, had been at bed rest for one hour in a room temperature of 18° C., the hands were blue (color 3), and the temperature of the fingers had fallen to 16.8° C. Nitroglycerin $\frac{1}{100}$ grain was then placed under the tongue, and the blood pressure, pulse, finger temperature, color, and microscopic appearance of the capillaries were recorded at five-minute intervals. The blood pressure fell slightly in five minutes. The pulse quickened by 20 beats. The color and temperature of the fingers as well as the appearance of the capillaries did not alter over a period of thirty minutes. There was a slight increase in the digital pulse volume which lasted but a short time. Adrenalin, 0.75 c.c. of a 1:1,000 solution, was then injected intramuscularly and the observations were continued for thirty-five minutes more. The blood pressure changed from 110/70 to 128/55 after fifteen minutes, and the pulse increased from 90 to 118 per minute. Again the skin color and temperature remained unchanged. The capillaries became questionably less distinct.

Much emphasis cannot be placed upon the results of an uncontrolled experiment of this kind. We feel, however, that the apparent nonreactivity of the skin vessels, particularly as regards adrenalin, may indicate a loss of their tonus.

Response of the Minute Vessels to Histamine.—Lewis has emphasized the fact that if histamine is pricked into normal skin which has cooled spontaneously to about 20° C., little or no rise of temperature occurs in the region of the resultant flare. Pricked into acrocyanotic skin at a similar temperature, histamine produces a rise of several degrees. Since this is one of the primary evidences upon which Lewis bases his conception of spasm of the skin arterioles as the cause of acrocyanosis, we have attempted, unsuccessfully, to confirm his observations. Our determinations are listed in Table I. Using the utmost care to duplicate Lewis' technique, we found a surprising lack of consistency in behavior of the normal and acrocyanotic skin, both in the same individual on repeated tests and in different individuals. We are unable to explain these inconsistencies satisfactorily. It may be that the skin of the normal individuals tested varied so extremely in sensitiveness to histamine as to overshadow any constancy in response on the part of acrocyanotic skin. We can testify, however, to the vivid pinkness of the flare when histamine is introduced into acrocyanotic skin which is spontaneously cool or made cold by immersion in water. According to our observations,

the pinkness of the flare is exaggerated by the surrounding blue tint but does not exceed, either in depth or tint, that present in normal skin under similar circumstances.

Studies to Differentiate Between the Effects of Centrally Mediated Vasomotor Tone and Local Response of the Vessels to Cold.—We have found it difficult to evaluate the importance of vasomotor impulses of central origin in producing the symptoms presented by our patients. One young man stated that his hands turned blue if his body became chilled from any cause or if he became emotionally disturbed. We verified these statements on several occasions. Mrs. H., in whom we may safely assume that the cervical ribs played little rôle in increasing vasomotor tones, gave a similar history. We have frequently seen her hands extremely blue under conditions in which the external temperature and lightness of clothing could not be invoked as the explanation. On one occasion, in the space of one minute, her fingers turned from pink to

TABLE I
TEMPERATURE RESPONSE TO INTRACUTANEOUS HISTAMINE

NORMAL					ACROCYANOSIS				
SUB-JECT	ROOM TEMP.	INITIAL FINGER TEMP.	FINAL FINGER TEMP.	DEGREES RISE	SUB-JECT	ROOM TEMP.	INITIAL FINGER TEMP.	FINAL FINGER TEMP.	DEGREES RISE
E. M.	18.2	18.8	19.6	0.8	S. H.	18.2	15.6	16.4	0.8
R. E.	18.2	18.8	19.0	0.2	S. H.	18.2	18.0	16.2	1.8
R. E.	14.4	18.8	20.0	1.2	D. R.	14.4	18.4	19.4	1.0
A. E.	18.2	19.2	25.0	5.8	S. H.	18.2	18.6	19.6	1.0
D. O.	17.8	19.4	19.7	0.3	S. H.	18.2	20.5	26.6	6.1
R. E.	23.8	21.0	27.0	6.0	S. H.	24.4	22.0	24.6	2.6
A. E.	18.2	22.6	30.4	7.8	D. R.	21.6	25.0	30.6	5.6

blue as the result of apprehension over an imminent hypodermic injection. The question is, therefore, whether these patients have a heightened vasomotor tone, or a normally responsive vasomotor apparatus which at times serves to accentuate a local vascular fault. This question is difficult to answer. Lewis has described the behavior of the acrocyanotic finger deprived of its vasomotor nerve supply by local-anesthetization of the ulnar nerve. We have studied the response to this procedure on four occasions in three patients. In each instance parallel observations were conducted upon a normal person. The results of a typical protocol are expressed graphically in Fig. 5. The liberty has been taken of adjusting the length of duration of anesthesia in the normal individual so that his temperature curve more nearly coincides, for purposes of comparison, with that of the acrocyanotic patient. The temperatures of the right second and fifth fingers of the former and of the right third and fifth fingers of the latter are expressed on the chart in terms of degrees below forehead temperature as better expressing the vasomotor gradient than would the actual readings. Before anesthesia the temperature of the patient's fingers was 12.5° C. below that of the forehead, whereas that of the normal fingers was only about 4° C. cooler. Within

ten minutes after anesthesia became manifest in the acrocyanotic hand, the temperature of the blocked finger had risen 8° . Color changes were carefully watched during this period because Lewis had found that the temperature of his patient's finger rose some 5° before pinkness appeared. He regarded this as indicating that, whereas the digital arteries opened quickly, the skin arterioles, initially in spasm, did not dilate primarily as a result of the nerve palsy but rather through the relaxing influence of the increased stream of warm blood coming to them from the larger vessels. This he accepts as additional evidence of arteriolar spasm in acrocyanosis. We can confirm this observation, as the color of our patient's fifth finger showed no sign of pinkness until the temperature had risen 7° . At this point the finger and ulnar side

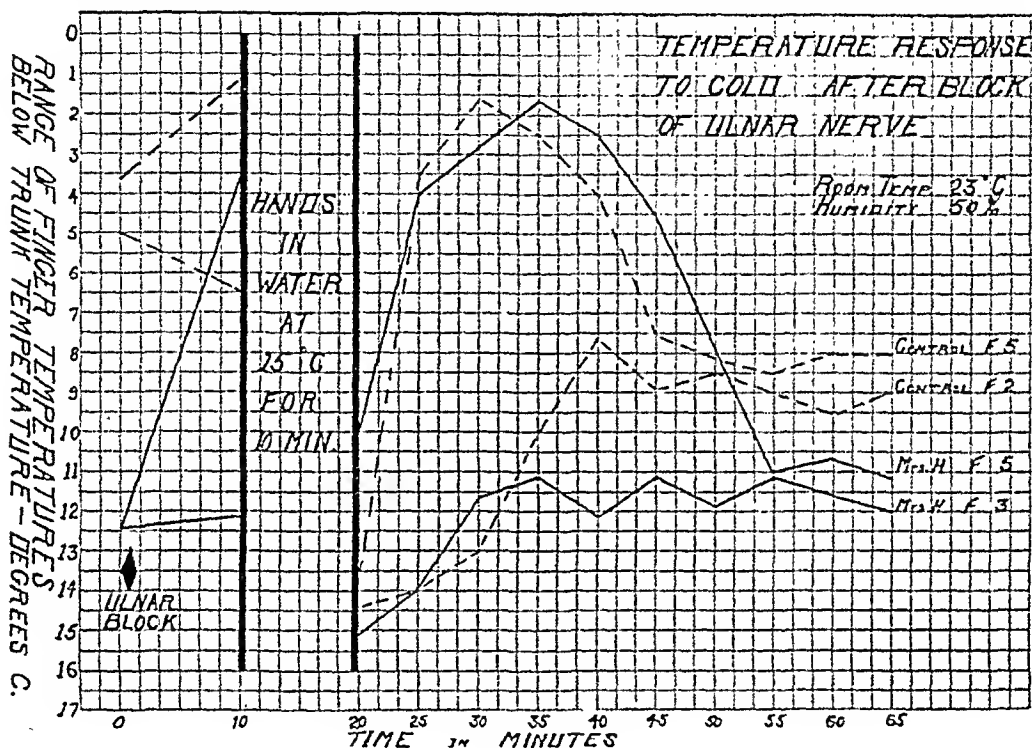


Fig. 5.

of the hand became vivid pink over a sharply demarcated area slightly exceeding the limits of anesthesia to pin prick. However, according to our observations there may be no appreciable change in color of the anesthetized normal finger even though its temperature exceed by 10° that of its neighbors. Therefore we cannot accept Lewis' deduction from this evidence without reservation.

When the temperature of our patient's anesthetized finger had reached a maximum, the hand was immersed in water at 15°C . for ten minutes and the color carefully observed. Whereas this finger retained a great share of its original color, the tint soon partook of a slight but definite blueness. Although its temperature was nearly at the preanesthetic level when read immediately upon withdrawal from the water, it rose 11.5°C . within five minutes—an effect parallel to that of a normal anesthetic

finger. By comparison, the temperature of the patient's third finger did not rise above the preanesthetic level.

These observations indicate that the major vessels of the acrocyanotic finger, when deprived of their vasomotor innervation, behave normally in response to local cold but that the minute skin vessels continue to exhibit a defective reaction.

In an attempt to study further the relative importance of centrally mediated or reflex vasomotor tone as against the purely local vascular reaction, the following experiment was devised: A patient with acrocyanosis was placed in a bathtub with water at a temperature of 21° C. and reaching to midchest, while the hands were immersed in a water bath for periods of ten minutes respectively at the following temperatures: 17 or 21°, 30°, and 40°. At the conclusion of each immersion period the color of the knuckles and finger nails together with the temperature of the fingers were immediately charted. After these readings the temperature of the bath water was increased to 30 and 40°, and the above observations were repeated. A similar experiment was conducted upon a normal individual. Results are given in Table II. Cyanosis of the finger nails was observed in the acrocyanotic patient at all immersion temperatures of bath water and hand bath, until the temperature of the former reached 40°, at which time plunging the hands into water at 17° failed to produce blueness. With the body bathed in water at 21 and 30°, however, immersion of the hands in water at 40° abolished the cyanosis of the fingers, the nails remaining blue. The highest skin temperature at which cyanosis of the finger nails persisted

TABLE II

SKIN COLOR RESPONSE TO VARYING ENVIRONMENTAL BODY AND HAND TEMPERATURES

TEMP. OF BATHTUB (° C.)	TEMP. OF HAND BATH (° C.)	COLOR OF HANDS	COLOR OF FINGER NAILS	SKIN TEMP. OF FINGERS (° C.)
<i>Acrocyanosis</i>				
21	21	2	9E	23.0
21	30	2	9E	25.0
25	40	1E	9C	29.0
30	17	2	9D	21.0
30	30	2	9E	26.0
30	40	1F	9D	29.0
40	17	1G	1G	22.0
40	30	1E	1E	30.0
40	40	1G	2H	33.0
<i>Normal</i>				
21	21	1E	1E	22.0
21	30	1D	1D	25.8
21	40	1D	1D	33.0
30	17	1G	1G	20.0
30	30	1D	1D	28.8
30	40	1F	1F	35.0
40	17	1G	1G	21.8
40	30	1F	1F	31.0
40	40	1H	1H	33.2

was 29°, and cyanosis of the hand, 26°. No cyanosis of the nails or hands of the normal individual was induced by any combination of bath-tub or hand bath temperatures, and the observed finger temperatures did not vary greatly from those of the patient.

The interpretation of these findings is perhaps as follows: With the patient's body bathed in water at a temperature below the average of the skin of his trunk, vasoconstrictor tone is reflexly heightened and accentuates the local vessel fault of the hands to the extent that cyanosis is not dissipated, even by the dilating influence of a hot hand bath. Conversely, when the body is bathed in water warmer than the skin, vasoconstrictor tone is apparently lessened to the extent that cyanosis can no longer be induced by cold. There is another possible explanation: that heat applied to the body, besides lessening or abolishing vasoconstrictor tone, stimulates vasodilator fibers which, as Lewis¹⁴ has shown, may reach the vessels of the arm. The fact that the acrocyanotic finger, deprived of its vasomotor nerve supply, may turn blue when immersed in cold water, whereas no blueness is observed in a hand bath of similar temperature when the body is warmed, is further evidence in this direction. In the first instance vasodilator fibers, as well as vasoconstrictors, are paralyzed; in the second, vasodilator fibers are intact and probably stimulated reflexly by warmth applied to the trunk. The validity of this conception would be strengthened by a study of the behavior of the anesthetized acrocyanotic finger under experimental conditions similar to those above. If such a finger became blue in cold water, even though the body were warmed, the phenomenon described would be due not to warmed blood reaching the hand, but rather to the intervention of vasodilator impulses. Unfortunately we have been unable to perform this experiment.

DISCUSSION

What is the exact nature of the vascular fault producing acrocyanosis?

In the first place, the theory based on obstruction to the venous drainage from the hand, either functional or structural in nature, has been disproved. As Lewis and Landis³ point out, Erben's observation that the subcutaneous veins are poorly filled was misinterpreted, as the smallness of the veins accompanied, rather than caused, coldness of the hands. The major arterial trunks of the hands, including the digital arteries, are likewise neither structurally nor functionally deranged sufficiently to explain the syndrome. The search therefore narrows to a consideration of the arterioles and minute vessels of the skin including the capillaries, collecting venules, and subpapillary venous network. Lewis and Landis regard an abnormal reactivity of the skin arterioles to cold as the cause of acrocyanosis. This conception is based fundamentally upon two lines of positive evidence. They cannulated the venous end of a capillary loop in the nail bed and, after obstructing the venous return by a pneumatic cuff about the arm, determined the length of time needed

for the capillary pressure to equal that imposed upon the veins by the cuff. Normally this adjustment required three to four minutes, but in their acrocyanotic patient the time was as long as eight minutes. This, they argued, indicated that the flow of blood into the capillaries was retarded by the arterioles. We are in doubt as to the interpretation of this observation. It seems possible that if the vascular bed just beyond the arterioles be widely dilated, the pressure of the inflowing arteriolar stream, even though normal, might be dissipated in a vascular area of greatly increased cross-section. Hence the rise in capillary pressure would be delayed until this area becomes engorged.

Their second line of positive evidence is the differing response to histamine of the acrocyanotic and normal skin at a similarly cool temperature. As already stated, they observed in the former a rise of several degrees in temperature in the region of the flare, while in the latter little or no rise was encountered. From this they argue that when the skin of an acrocyanotic hand and a normal hand are both at a spontaneously cool temperature, the former is so primarily because the skin arterioles are in spasm, whereas the coolness of the normal skin is traceable to constriction of the digital arteries. In the one instance, relaxation of the skin arterioles by histamine produces a rise in temperature indicative of increased arteriolar blood flow; in the other, the larger arteries are not relaxed by histamine, and hence increase in arteriolar blood flow is negligible. We were unable to verify these observations and so are not convinced of the validity of Lewis' hypothesis.

Our interpretation of the available evidence leads to the conclusion that the primary vascular fault in acrocyanosis is a dilatation and refractoriness to stimuli of the capillaries and venules of the skin. The state of engorgement of these minute vessels is a passive result of the amount of the blood brought to and leaving them. The evidence may be briefly summarized. There is direct morphological demonstration that these vessels are dilated. The distribution of this disorder over the most dependent portions of the extremities, where the minute vessels are subjected to hydrostatic pressure in the veins, with its tendency to cause engorgement of even a normal hand, is well explained on this basis. The hands of our patient never exhibited an entirely normal appearance except when elevated above her head, a position which obviously favors drainage of blood from the minute vessels. With the hands dependent, pressure upon the skin left a pale area which was slow to fill. This might be due to slowed arteriolar inflow but more probably indicates a larger cross-section of empty vessels to be filled than is present in a normal skin under similar circumstances. As regards the nonreactivity of the capillaries to stimuli, we could not determine that in our patient there was any change in their caliber in response to cold, heat, adrenalin, or nitroglycerin. These observations, however, should be repeated and extended.

We do not wish to imply that there is no abnormality of reaction on the part of the arterioles in acrocyanosis, but only that in our opinion this is not the primary fault. Slowing of the arteriolar blood flow through any cause, be it a reaction to cold, to heightened vasomotor tonus, or to drugs, would materially exaggerate this fault, particularly if at the same time the minute vessels are subjected to the effects of hydrostatic pressure through the veins. That increased irritability of the vasomotor system may play a rôle in the production of this syndrome can hardly be affirmed or denied from the available evidence.

We should like to add that acrocyanosis should not be regarded necessarily as evidence of disease elsewhere in the body, as is somewhat commonly assumed.

SUMMARY

1. Experimental studies dealing with the nature of the circulatory mechanism which produces acrocyanosis are reported.

2. The evidence indicates that the primary vascular fault lies in dilatation and lack of response to stimuli of the minute skin vessels. The clinical picture depends upon the passive filling of these vessels as influenced by the amount and nature of the blood in them.

3. The rôle played by the tonus of the sympathetic nervous system, as opposed to the local reaction of the vessels to thermal stimuli, is discussed. Observations dealing with the effects of certain vasoactive drugs upon the vascular fault are presented.

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DOUBLE AORTIC ARCH WITH TOTAL PERSISTENCE OF THE RIGHT AND ISTHMUS STENOSIS OF THE LEFT ARCH: A NEW CLINICAL AND X-RAY PICTURE

REPORT OF SIX CASES IN ADULTS*

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THE diagnosis of congenital anomalies of the heart and large vessels is still a difficult problem, and it is only in exceptional cases that we are able to make a correct diagnosis in vivo and to confirm it by post-mortem examination. The fact that we have so few cases with careful clinical, roentgenological, and pathological findings makes it almost impossible at present to state definite clinical or roentgenological signs for a given anomaly. The six cases of double aortic arch (two confirmed by post-mortem examination) which I wish to report illustrate the great value of the x-ray in the diagnosis of such malformations. The opportunity of studying the first case clinically, roentgenologically, and at autopsy enabled the writer to recognize five more cases, and to establish a new clinical and x-ray picture by which the diagnosis of persistent right and left aortic arch can be made. This type is a form in which the right aortic arch takes its course over the right bronchus, then behind the trachea and esophagus. The left arch also persists, but with stenosis or atresia in the isthmus region.

The first case of this anomaly ever recognized during life was seen and diagnosed by the writer at the First Medical Clinic of the University of Vienna on Aug. 25, 1925. The diagnosis was confirmed at autopsy. The findings were presented before the Vienna Roentgen Society in October, 1925, and published in the *Wiener Archiv für innere Medizin* in 1926, along with two other cases observed clinically and diagnosed *intra vitam* but without autopsy. Since then the writer has added observations of three other cases with characteristic clinical signs and the same x-ray findings. The last case (Case 6 in this publication) was confirmed in every detail at autopsy. This makes a total of six cases observed, of which two were confirmed post mortem. We shall therefore discuss the embryological development of the aorta and its anomalies before describing this type of persistence of the right and left aortic arch with partial obliteration of the latter. This anomaly is of great interest from the evolutionary standpoint since it represents a reversion to the reptilian type of double aortic arch. Its clinical significance will be discussed later.

Most of the cases described in the anatomical and pathological literature have been cases of right aortic arch in which the descending aorta

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begins its downward course on the right side. This is the more usual form and has been described roentgenologically by Assmann in three cases. A study of the malformations of the great vessels also reveals the existence of double aortic arch, eight cases of which Poirier collected in 1896. In these cases the right or posterior aortic arch is usually the larger, the left or anterior arch the smaller. The trachea and esophagus lie between the two arches. The six cases which we shall describe belong to that type of double arch in which the large right arch lies retro-esophageally and the small anterior left arch has undergone stenosis in the isthmus region. A right aortic arch may also be pulled to the left behind the trachea and esophagus by the ductus arteriosus when the left fourth arch is incomplete. In such cases the left descending dorsal aortic root is short or absent so that the condition of double arch does not persist as such.

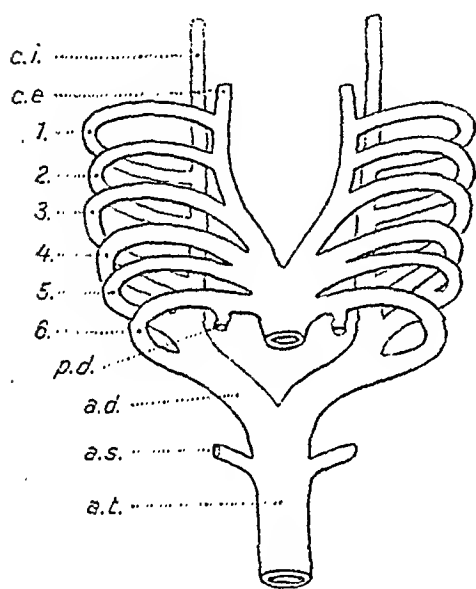


Fig. 1.

Fig. 1.—Diagram of the development of the large arteries:

c.i., internal carotid
c.e., external carotid
1 to *6*, aortic arches
p.d., right pulmonary

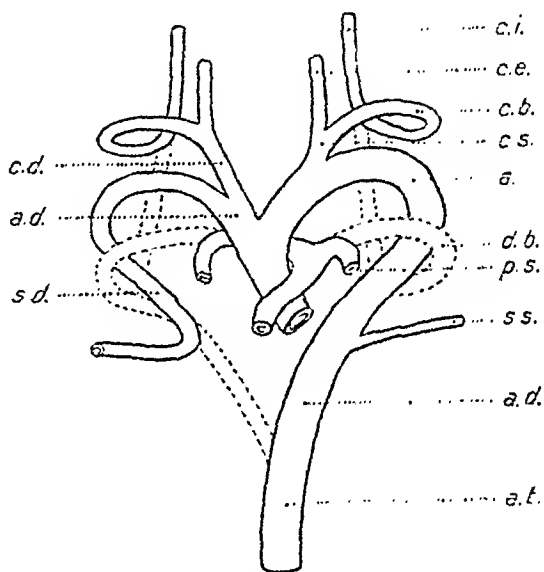


Fig. 2.

Fig. 2.—Diagram of the development of the aorta and large arteries:

c.i., internal carotid
c.e., external carotid
c.b., carotid arch
c.s., left carotid
a., aorta
d.b., ductus Botalli
p.s., left pulmonary

a.d., dorsal aortic root
a.s., subclavian artery
a.t., thoracic aorta.

s.s., left subclavian
a.d., dorsal aorta
a.t., thoracic aorta
c.d., right carotid
a.d., right innominate
s.d., right subclavian.

THE EMBRYOLOGICAL DEVELOPMENT OF ANOMALIES OF THE AORTA

For an understanding of the anomalies of the aorta we must first consider its normal development. In the third week of embryonic life we see the beginning of the development of the six aortic arches. The primitive aortic arch becomes the first branchial artery when the other five branchial arches develop between the primitive ascending aorta and

the primitive descending aorta. Thus the trunk goes over into six arches on each side. They do not all develop at the same time and are not all present at the same time. Some begin to disappear before others have appeared. The fifth soon recedes so that the sixth primitive arch later appears as the fifth, and the first and second also disappear. The remaining three are concerned in the development of the permanent vessels. The arches unite caudad to form two dorsal descending aortas, which fuse to form the common descending aorta (Fig. 1). From the sixth arch there grows on each side a main branch of the pulmonary artery. The portion of the right arch distal to the place of origin of the right branch disappears, while the corresponding portion of the left arch forms the ductus arteriosus Botalli. The left fourth arch forms the permanent aortic arch, the right the innominate artery and the beginning portion of the right subclavian artery. The dorsal communicating portion between the third and fourth arches disappears on both sides. The third arch forms the internal carotid, and the cranial persisting portion of the ascending aorta forms the external carotid. Finally the communication between the right fourth arch which forms the innominate artery and right subclavian and the permanent descending aorta disappears (Fig. 2).

With this brief discussion and a study of the two figures which illustrate the normal development, we shall have no difficulty in understanding the anomalies of the aorta and the large arteries. There are four chief types: (1) double aortic arch, (2) right-sided aortic arch, (3) absence of the aortic arch, and (4) origin of the right subclavian artery from the descending arch.

Double Aortic Arch

The ascending aorta may divide into two convex ascending aortas and arches which give off a subclavian, the external and the internal carotid, and then combine to form the descending aorta. Or, the ascending aorta may be normal and only the arch divided (Fig. 3). There is then an anterior and a posterior arch. The anterior or left arch originates from the left fourth branchial artery, and the posterior from the right. In these cases the trachea and esophagus usually lie between the two arches. We shall see that the anomaly of which we are describing six cases is closely related to this group. In double arch the anterior or left arch is usually smaller than the posterior or right arch.

Right-Sided Aortic Arch

This anomaly, which is the normal aortic type in birds, results from the persistence of the right fourth arch and right descending aortic root, while they in part or completely disappear on the left side (Fig. 4). The arch of the aorta goes over the right main bronchus and downward on the right side, as a rule; it may, however, go behind the trachea and esophagus, as in our six cases.

In most cases of right-sided aorta the arch and part of the descending aorta are located to the right of the vertebral column. With this abnormal position of the arch there are also abnormalities in the course of the left ductus Botalli because the right ductus almost always disappears. Although the aorta in these cases, as in birds, chooses the right

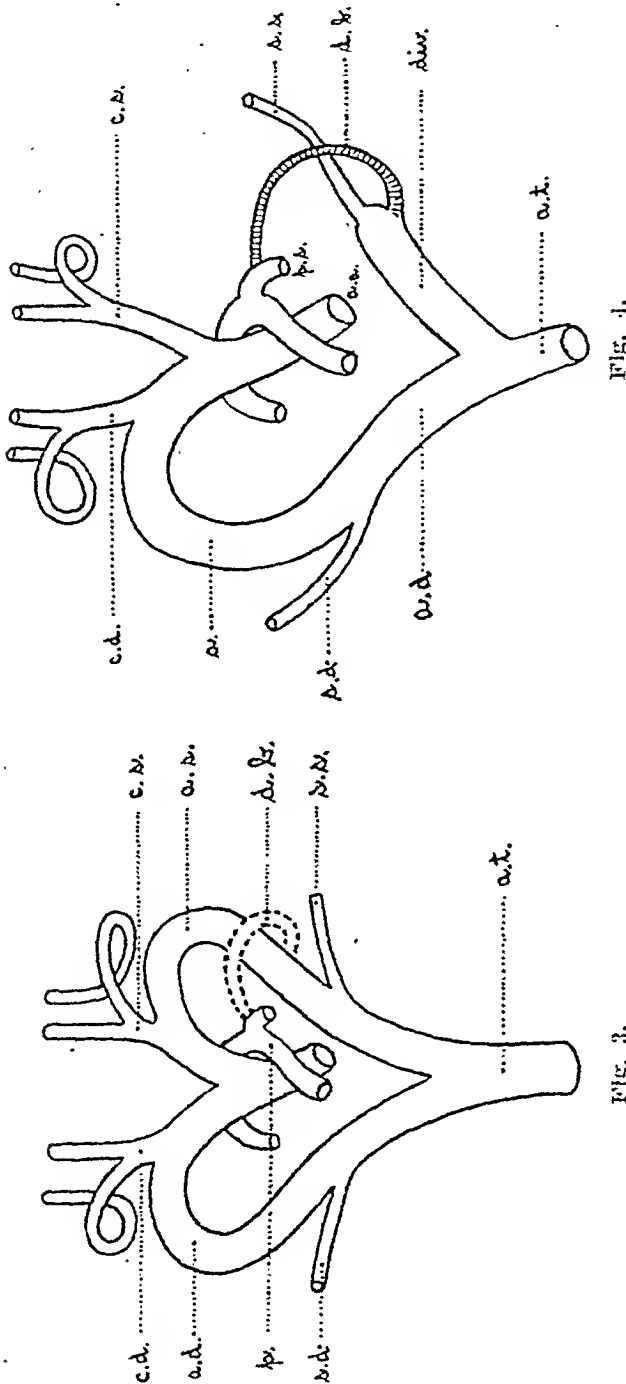


Fig. 3.—Diagram of the development of double aortic arch:

c.d., right carotid
a.d., right aortic arch
(posterior arch)
p., pulmonary artery

s.d., right subclavian
c.s., left carotid
a.s., left aortic arch
(anterior arch)

Fig. 4.—Diagram of the development of the more common type of right-sided aorta (persistence of the right aortic arch):

c.d., right carotid
a., right-sided aorta
s.d., right subclavian
a.d., descending aorta
d.b., ductus Botalli

div., diverticulum (rest of left descending dorsal aortic root)
c.s., left carotid

d.b., ductus Botalli
s.s., left subclavian
a.t., thoracic aorta.

Fig. 4.—Diagram of the development of the more common type of right-sided aorta (persistence of the right aortic arch):

p.s., left pulmonary
a.d., ascending aorta
s.s., left subclavian
a.t., thoracic aorta.

fourth arch and the right descending root, still the left ductus Botalli persists as in mammals. The result is that the ductus Botalli remains in close connection with the left descending aortic root and the left subclavian artery.

The left subclavian artery takes a very characteristic course in some of these cases. Holzapfel in 1899 collected twenty-one cases of abnormal

left subclavian artery in cases of right-sided aorta. In all, the left subclavian was the last branch of the right-sided aorta. In almost all the cases the beginning portion of the left subclavian (left descending dorsal aortic root) was enlarged. This diverticulum-like portion usually runs to the left behind the esophagus and gives off the left subclavian artery, and communicates with the left ductus Botalli (Fig. 4). The writer described such a case of right-sided aorta with retroesophageal left descending aortic root and left subclavian in 1926. The typical location for the left descending root is the place where the arch goes over into the descending aorta, usually at the level of from the second to the fourth thoracic vertebra. This constancy of location of the left subclavian is due to its close relation to the ductus Botalli. In cases of abnormal right subclavian artery this close relationship does not exist, and hence the origin of abnormal right subclavians is quite variable. If retrogressive changes occur in the left dorsal aortic root then the abnormal left subclavian may originate from the left ductus Botalli. In 1922 Goldbloom also collected examples of anomalous right subclavian artery.

Absence of the Aortic Arch

The arch of the aorta may be entirely absent, or only the isthmus (portion lying between the origin of the subclavian artery and the insertion of the ductus Botalli) closed or entirely absent. There is then no communication between the ascending and the descending aorta. When the fourth arch and the lateral communicating branch between the fourth and sixth arch become obliterated, then the sixth arch and left descending aortic root may remain open. The ascending aorta then supplies the vessels of the head and the right subclavian, and the open ductus Botalli goes over into the descending aorta on the left side.

TOTAL PERSISTENCE OF THE RIGHT AORTIC ARCH AND ISTHMUS STENOSIS OF THE LEFT AORTIC ARCH

The six cases which we shall describe represent an intermediate type between persistence of both aortic arches and persistence of the right aortic arch. We have in our cases the persistence of both aortic arches, total of the right which has the size of a normal aorta, and partial occlusion of the left arch which may be looked upon as an isthmus stenosis. We shall see that it is the persistence of the left aortic arch (in the form of the left subclavian artery, a short occluded vessel, and the left descending dorsal aortic root) which is responsible for the location of the arch behind the trachea and esophagus in our cases. The writer was able to demonstrate in the roentgenograms of the patients not only the right-sided retroesophageal aorta but also the shadow of the left dorsal aortic root which looks like a diverticulum and lies behind the esophagus. We have therefore named this anomaly "right-sided retro-

esophageal aorta," or "total persistence of the right and partial stenosis of the left aortic arch." This is in contrast to a type of right-sided aorta described by Assmann.

The three cases of so-called high right-sided aorta (*hohe Rechtslage der Aorta*) described by Assmann represent the type of right-sided aorta with right-sided arch which we have already discussed (Fig. 4). The name used by Assmann is unsatisfactory because it does not explain the nature of the anomaly and can easily be confused with right-sided displacement of a normal aorta by pathological conditions in the chest, such as fibroid pulmonary processes, exudates, pneumothorax, tumors, etc. I therefore suggested in 1926 the term "right-sided aorta," or persistence of the right aortic arch instead of "high right position of the aorta." In the cases described by Assmann, the aorta runs over the right bronchus and the arch remains on the right side. We have already seen that this anomaly represents most of the cases of right-sided aorta described by anatomists and pathologists. The x-ray picture is that of an aortic knob on the right side in the right sternoclavicular region. The aortic band usually seen in the right oblique position is visible in the left oblique as a pulsating curved shadow over the right bronchus. In the right oblique position the aortic band is lighted away by the trachea and left bronchus except for a small narrow strip just above the heart. The x-ray examination of the esophagus is not mentioned in the three cases. From the above discussion of this anomaly we can see that this is very important because in this form of right-sided aorta with right-sided arch the left descending dorsal aortic root or the left subclavian artery or ductus Botalli is found behind the esophagus.

Because anomalies of the heart, as well as of the aorta, were found in Assmann's cases he assumed that right-sided aorta or persistence of the right aortic arch is associated with cardiac defects. Two of his cases had a subaortic ventricular septum defect with the aorta riding the defect. Assmann looked upon these as representing a definite type in which the aorta is usually wider and the pulmonary artery narrower than normal. The third patient possessed an abnormally narrow aorta which passed upward from the left ventricle over the right bronchus. There was also a large auricular septum defect. Dietlen, who described no cases of his own, states in his book on x-ray diagnosis of the heart that right-sided aorta occurs only in connection with other defects. Mohr also concludes that a *hohe Rechtslage* indicates the existence of ventricular septum defect. Sprong and Cutler point out that associated anomalies were common in their series of thirteen cases of right aortic arch with left innominate artery but no *situs inversus viscerum*. We shall see from our cases that persistence of the right aortic arch can occur without any malformations whatever in the heart. In our six cases there was no evidence in any of functional or organic cardiac disturbance: the hearts were all normal in size and form. The patients were all adults

and in all of the cases the anomaly was an incidental finding during a routine physical and fluoroscopic examination of the chest. In other words it produced no subjective symptoms. The two necropsied cases revealed a normal heart free from any anomalies. A persistence of the right aortic arch instead of the left is itself no cause for the existence of cardiac anomalies and bears no necessary relation to the embryologic development of the heart. We have seen ten hearts with persistence of the right aortic arch in various pathological museums and at autopsies and in nine of the ten the heart was entirely normal. A study of the literature reveals many anatomical specimens of right aortic arch with normal heart.

We shall see that there is a marked difference between the x-ray findings in right-sided aortic arch of the Assmann type and those in right-sided retroesophageal aortic arch first diagnosed by me.

This type of right-sided retroesophageal aorta belongs to the group of cases recorded in the older literature under the title "dysphagia lusoria," a term which should be dropped because of its inaccuracy. This phrase was used by Bayford in 1789 to describe a case of dysphagia which he considered to be due to the pressure of an anomalous right subclavian artery on the esophagus. Relatively few of such anomalies cause a dysphagia. In only one of our six cases in which the aorta is located behind the esophagus and displaces it forward and to the left was there any disturbance of swallowing. This one patient had a carcinoma of the cardia of the stomach. Had an aneurysm of the arch developed there would undoubtedly have been a dysphagia. Perhaps the term "arteria lusoria, with or without dysphagia" would be better for these cases.

CASES OF RIGHT-SIDED RETROESOPHAGEAL AORTA

(TOTAL PERSISTENCE OF THE RIGHT AORTIC ARCH AND PERSISTENCE WITH PARTIAL STENOSIS OF THE LEFT AORTIC ARCH)

CASE 1.—The patient, H. H., a man fifty years old, entered the First Medical Clinic of the University of Vienna on Aug. 19, 1925. His illness dated from June of the same year when he developed an acute angina with a fever of 39°C., lasting ten days. After an interval of four days he had a second attack lasting five days. Two weeks later the third attack brought him to the hospital. He had painful swelling of both ankles. The pains in the legs were so severe that walking was impossible. After a careful physical examination, which revealed no cause for his fever, the patient was sent to the x-ray laboratory for an examination of the chest. Here the writer saw him on Aug. 22, 1925.

The fluoroscopic examination revealed a darkening of both apices with a few small dense spots in the right infraclavicular area. There were some calcified glands in both hilums. The examination of the heart revealed an unusual picture such as the writer had not previously seen. Attention was immediately attracted to the presence of a dense shadow which ran upward from the right heart border just to the right of the sternum to the region of the head of the right clavicle, and to the

absence of the normal aortic knob to the left of the sternum. A careful examination with a small diaphragm showed the shadow to the right of the sternum to be sharply outlined and to run upward to the level of the right clavicle where it described a curve to the left and was lost in the shadow of the spine. This shadow showed a very distinct pulsation synchronous with the ventricular systole. On the left side there was found only a faint suggestion of an aortic knob instead of the normal prominent knob produced by the descending portion of the aortic arch.

The next thing that attracted attention was the fact that the trachea was displaced to the left, instead of to the right as is found normally (Fig. 5). The heart



Fig. 5.—Right-sided retroesophageal aorta (persistence of the right aortic arch). The aorta runs upward on the right side, above the right bronchus, then behind the trachea and esophagus (Case 1, total persistence of the right, isthmus stenosis of the left aortic arch).

itself appeared normal except for a slight enlargement of the left ventricle. In the first (right anterior) oblique position a very interesting and new picture presented itself. The trachea, instead of running downward parallel with the spine, described a semicircular curve forward at the level of the upper border of the clavicles. It reached its maximum distance from the spine at a point behind the middle of the manubrium (Fig. 6). Just below this level the trachea divided into its two main branches. An examination of the esophagus with a barium paste showed a similar

circular displacement forward and to the left of the esophagus at the same level. A distinct pulsation could be seen against the posterior wall.

There was no aortic knob visible in front of the trachea in the first oblique position. There was found, however, a round shadow about $1\frac{1}{4}$ inches in diameter directly behind the displaced trachea and esophagus. This shadow showed a distinct



Fig. 6.—Total persistence of the right aortic arch, isthmus stenosis of the left aortic arch. The same patient as in Fig. 5, showing right anterior oblique view. The aortic knob is seen behind the trachea, which is displaced forward. In this retrotracheal knob can be seen the round shadow of the rest of the left descending dorsal aortic root.

systolic pulsation. The shadow was separated from the heart below by the trachea and right main bronchus. In the retroesophageal and retrotracheal shadow just described there can be seen a smaller, round, more intense shadow about $\frac{3}{4}$ inch in diameter.

In the second (left anterior) oblique position we saw the ascending aorta producing a wide pulsating shadow to the right of the trachea. It described a convex border and extended upward to the region of the upper border of the left clavicle, then ran downward to form the descending aorta which was visible in this position in front of the spine.

The diagnosis made on August 25 after an examination of the photographs was: so-called high, right-sided position of the ascending aorta, which is distinctly visible above the right heart border and to the right of the sternum, and runs over the right bronchus instead of the left. In the first oblique position the ascending aorta

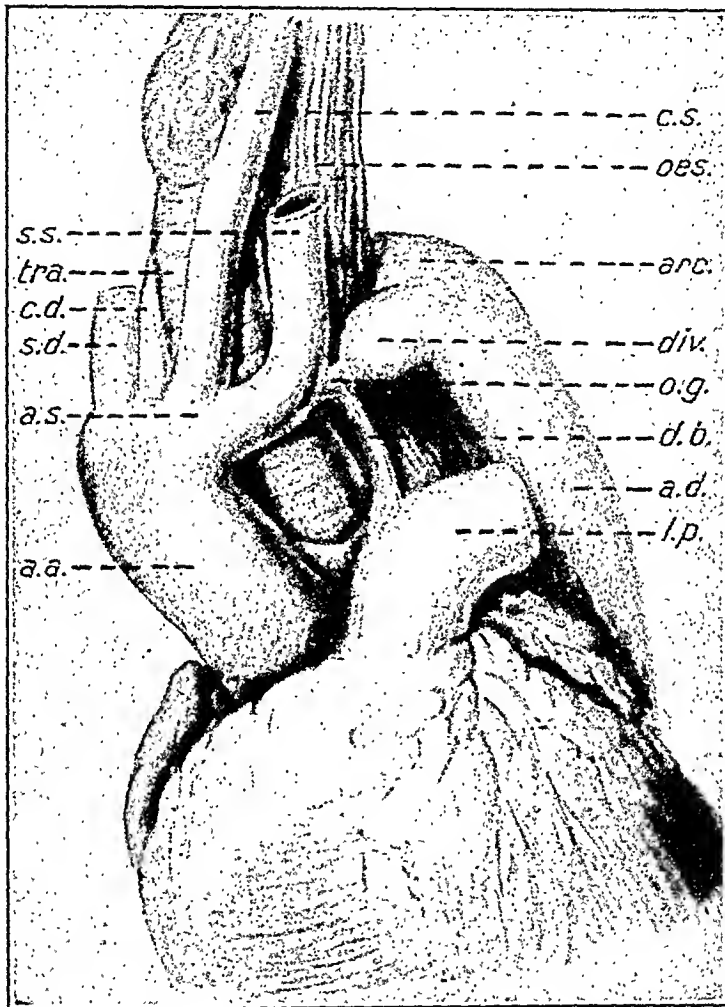


Fig. 7.—Drawing of heart and aorta from Case 1, viewed from the left side. Here we see the right-sided aorta running over the right bronchus, then behind the trachea and esophagus. The ring around the trachea and esophagus formed by the right-sided aorta and the left aortic arch (left subclavian artery, occluded short vessel, and diverticulum) is distinctly visible.

c.s., left carotid
oes., esophagus
arc., arch of aorta
div., diverticulum
o.g., occluded vessel
d.b., ductus Botalli
a.s., left innominate

a.d., descending aorta
l.p., left pulmonary
s.s., left subclavian
tra., trachea
c.d., right carotid
s.d., right subclavian
a.a., ascending aorta.

is partly lighted away by the trachea and right bronchus. No aortic knob is visible in front of the trachea. A round pulsating shadow lies behind the trachea and esophagus and displaces these forward and to the left. This shadow most likely represents the aortic arch behind the trachea and esophagus.

Blood and spinal fluid Wassermann tests were negative, also tests for typhoid and paratyphoid bacilli. The patient died on Sept. 17, 1925. The autopsy was per-

formed by Dr. Feller at the Pathological Institute of Prof. Maresch. Death was due to a generalized periarteritis nodosa. We shall describe only the heart and great vessels which are of interest here.

There was hypertrophy of the left ventricle. Otherwise, the auricles and ventricles were entirely normal. There was no congenital anomaly of the heart; the auricular and ventricular septa were normal; and the foramen ovale was closed. All of the valves were normal. An examination of the aorta revealed a right-sided aorta which ran upward over the right bronchus and then horizontally and downward behind the trachea and esophagus. The trachea and esophagus were displaced forward and to the left. There was a deep impression in the posterior wall of the esophagus which formed the bed for the aortic arch. At the beginning of the descending aorta and behind the left posterior border of the esophagus there was a diverticulum, or pouch, which projected from the anterior surface of the aorta. The diverticulum also made a depression in the left margin of the esophagus to which it was attached by loose connective tissue. The pouch was 1.8 cm. in diameter and 1.5 cm. in length. From this diverticulum of the aorta two occluded vessels branched off, one to the left subclavian artery and the other to the left branch of the pulmonary artery. The former corresponded to the isthmus of the normal left-sided aorta and the latter represented the ductus Botalli. A short distance below the diverticulum the aorta ran downward and medially, forming the thoracic aorta. The right-sided retroesophageal aorta was of normal size. The valves were normal. The first branch of the ascending aorta was a short left innominate artery which divided into the left subclavian and left carotid. The second branch was the right carotid, and the third branch the right subclavian. After giving off these three branches the aorta ran in the angle between the trachea and right bronchus and then curved to the left behind the trachea and esophagus. Where the arch went over into the descending aorta lay the diverticulum already described (Fig. 7).

We thus see that we are dealing in this case with a persistence of the right aortic arch which runs over the right bronchus and behind the trachea and esophagus. The shadow which was found behind the trachea and esophagus represents a retrotracheal and retroesophageal aortic knob. The trachea and esophagus are therefore displaced forward and slightly to the left. This picture is so characteristic that when it has once been seen it can be recognized immediately. The finding which is diagnostic of this anomaly is the characteristic displacement of the esophagus at the level of the arch, and this is clearly visible in the first oblique position. In fact, the dislocation of the trachea and esophagus to the left is even visible on posteroanterior fluoroscopic examination. We shall see later that there are other anomalous arteries which may displace the esophagus, but they usually occur below the level of the aortic arch.

The circular, more intense shadow seen on the photographs in the retroesophageal aortic knob in the first oblique position represents the diverticulum which we found on the anterior wall of the aorta where the arch goes over into the descending aorta. The size of the shadow, the sharp outline, and the location behind the trachea at the level of its bifurcation make this the correct interpretation of this shadow. The diverticulum is, as we shall see, the left descending dorsal aortic root to which the ductus Botalli and occluded isthmus are attached.

The characteristic x-ray findings in our case of right-sided retroesophageal aorta are therefore:

1. A sharply outlined shadow with systolic pulsation to the right of the sternum, which begins at the fourth right intercostal space, goes

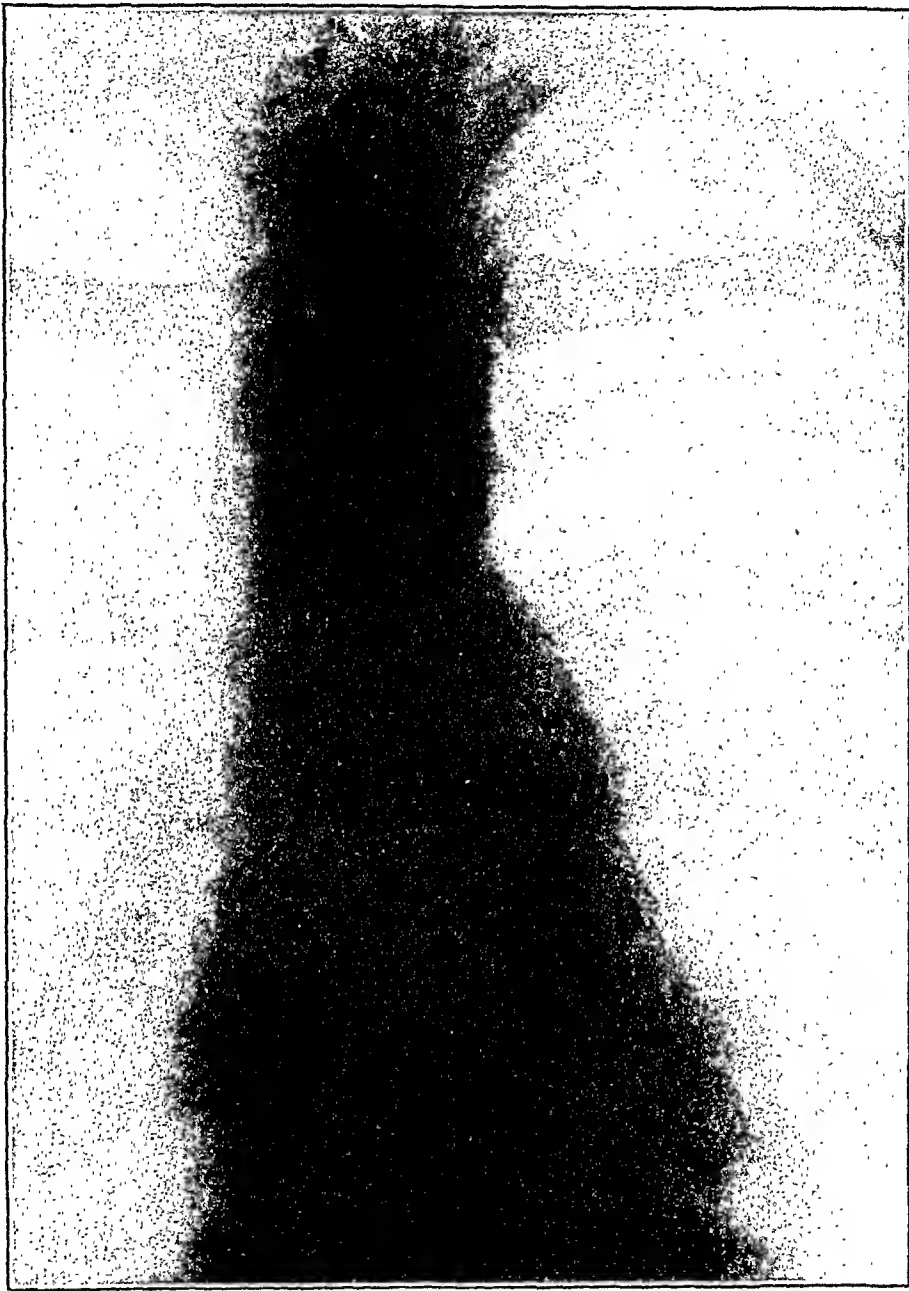


Fig. 8.—Right-sided retroesophageal aorta (persistence of the right aortic arch) as seen in Case 2. Note the ascending aorta to the right of the esophagus, which is displaced to the left. There is no aortic knob on the left side. The pulmonary artery appears prominent.

upward in a very slight curve to the region of the right sternoclavicular joint, then in a convex curve to the left and downward producing a very small aortic knob to the left of the sternum. In younger individuals no knob may be visible on the left side.

2. In the first oblique position no aortic knob in front of the trachea, but instead a retrotracheal and retroesophageal aortic knob separated from the heart shadow by the trachea and right bronchus.

3. In this knob a circular darker shadow which represents the diverticulum or pouch (left descending dorsal aortic root). This shadow is not always demonstrable.

4. Dislocation of the trachea and esophagus forward in a semicircle and slightly to the left.

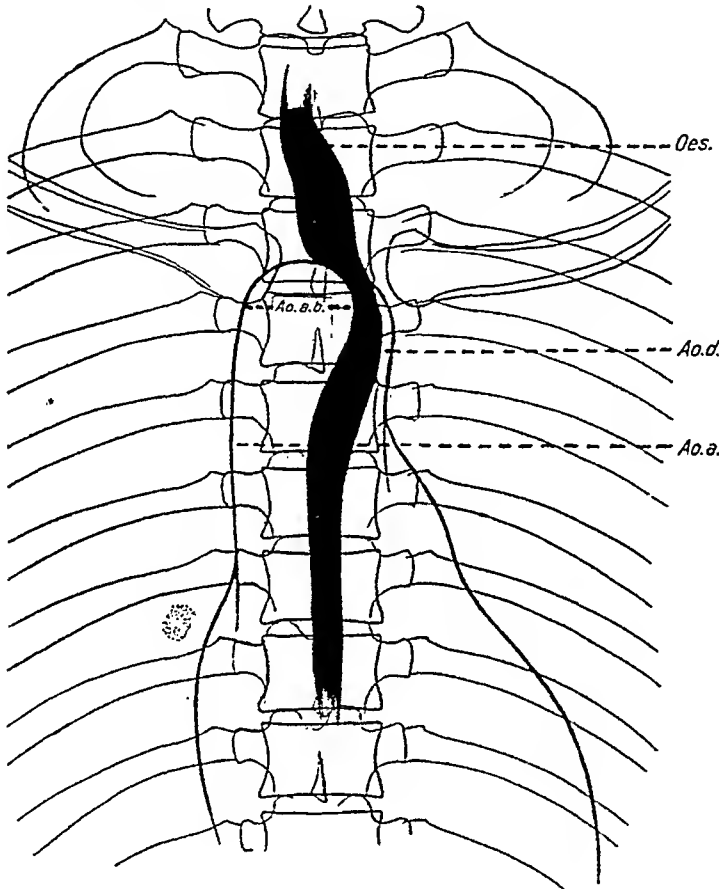


Fig. 9.—Explanatory sketch for Fig. 8:

Ao.a.b., width of ascending aorta
Oes., esophagus

Ao.d., descending aorta
Ao.a., ascending aorta.

5. Distinct systolic pulsation of the retrotracheal aortic knob shadow.

6. In the second oblique position a wide ascending aortic band visible to the right of the trachea and above the right bronchus.

CASE 2.—On Oct. 17, 1925, a young woman, aged twenty-five years, was sent to us for a fluoroscopic examination of the chest. This was required of her when she made application for a position as nurse in a children's hospital. She was a normally developed, healthy young woman with no cardiac or other complaints. On fluoroscopic examination the writer was at once impressed with the similarity between the findings and those just described in Case 1. The absence of the normal aortic knob on the left side, the characteristic shadow to the right of the sternum with its systolic pulsation and the slight displacement of the trachea to the left led us to think at once of the possibility of a right-sided retroesophageal aorta.

Having discovered the characteristic circular displacement of the esophagus at the level of the arch we at once gave the patient some barium paste to swallow and found the exact picture observed in our first case. The esophagus described a curve forward and to the left, then gradually returned to its normal position (Figs. 8, 9, 10, and 11).

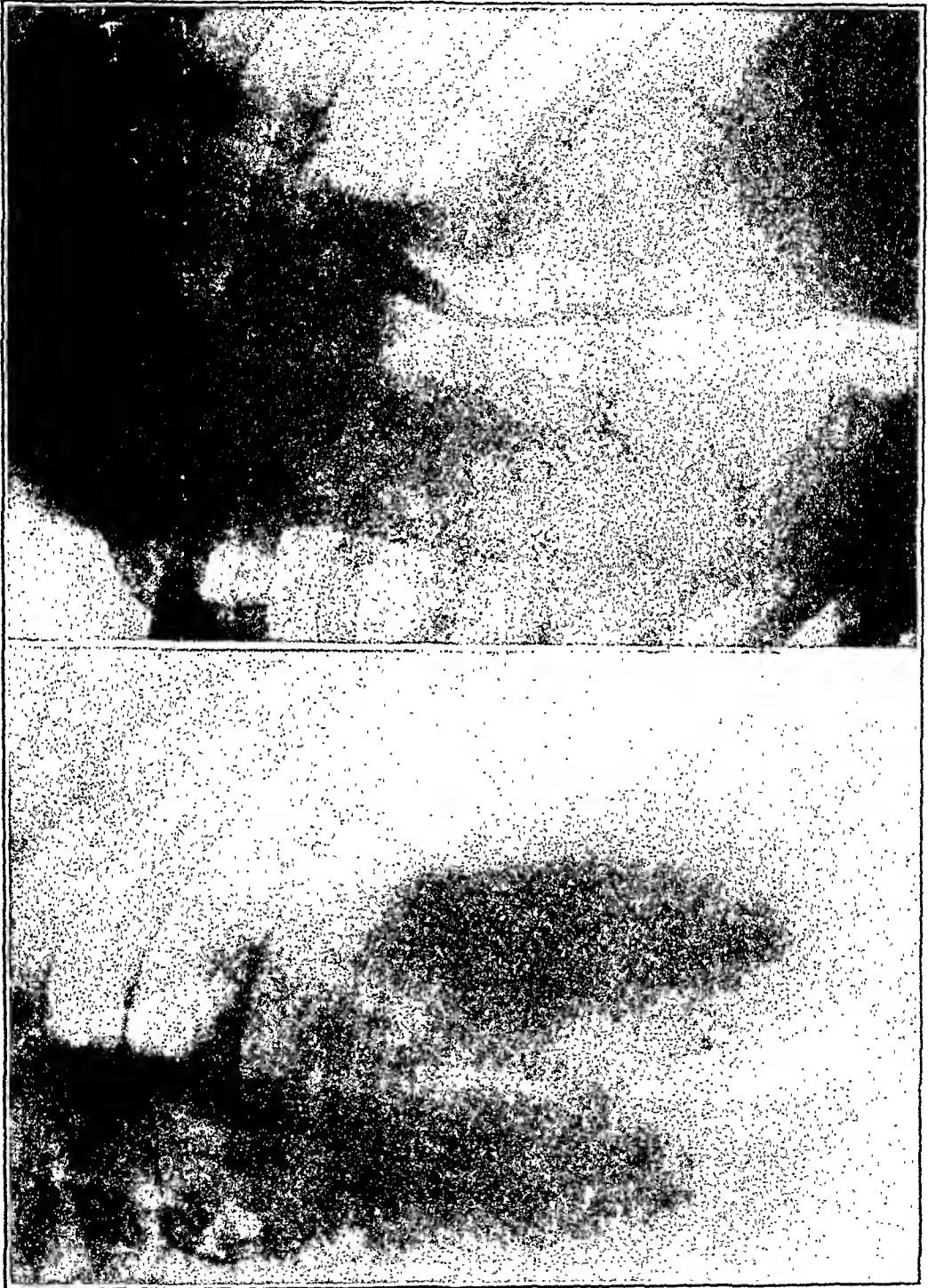


Fig. 11.

Fig. 10.

Fig. 10.—Right-sided retroesophageal aorta (Case 2) in the first oblique position. The trachea is displaced forward, and to the left, and the aortic arch lies behind the trachea. In the aortic knob a round shadow similar to that found in Case 1, is visible. This may be the diverticulum (left dorsal aortic root).

Fig. 11.—Right-sided retroesophageal aorta (Case 2) in the first oblique position, with the esophagus filled with barium. The esophagus is displaced forward in a curve at the level of the aortic arch, and reveals a distinct pulsation produced by the aorta against its posterior wall. This finding is characteristic of the anomaly.

We see from Figs. 8 and 9 that we have in these cases a method of determining the width of the ascending aorta by filling the esophagus with barium. With the normal aorta Krenzfuhs has described this method for measuring the descending arch.

CASE 3.—On Feb. 4, 1926, the writer had the opportunity of seeing a third case of total persistence of the right aortic arch with the aorta behind the trachea and esophagus. The patient was a young man twenty-seven years old. He had a colloid goiter with marked enlargement of the thyroid gland and bilateral apical tuber-

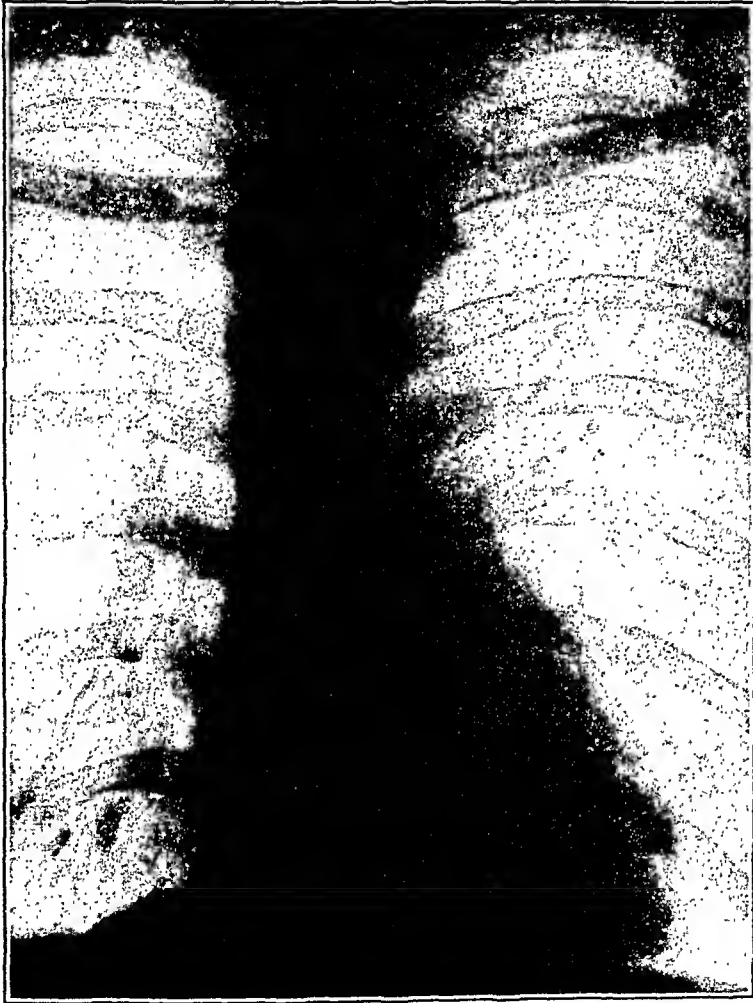


Fig. 12.—Case 3. Right-sided retroesophageal aorta. Note again the shadow of the ascending aorta which runs upward on the right side to the upper border of the clavicle. There is no aortic knob on the left side, and the pulmonary artery therefore appears prominent. The esophagus is displaced to the left by the descending arch. The heart is normal.

culosis. Again the x-ray findings were identical with those already described, except that the writer was not able to demonstrate to his satisfaction the round shadow of the diverticulum in the retroesophageal aortic knob. The other findings corresponded exactly with those which we have already detailed. The esophagus and trachea revealed the same diagnostic displacement. It is interesting that in the second and third cases in younger individuals the aortic knob was not at all visible on the left side. As a result, the pulmonary artery was more prominent than normally because it was not partly covered by the descending portion of the aortic arch (Fig. 12).

In this patient also the heart appeared normal, and the electrocardiogram was normal. There were no cardiac or other symptoms. There was no difficulty in swallowing.

In the second and also in the third case the writer found a clinical symptom which may aid one in suspecting the presence of right-sided aorta. In these two cases it was found on auscultation that the second aortic tone is heard best over the head of the right clavicle instead of in the usual place. The second pulmonary tone is found in normal position so that it is easy to differentiate the second aortic from the second pulmonary tone. The second aortic tone was louder than the second pulmonary tone in both cases. This finding is easily explained by the position of the right-sided aorta and its close proximity to the surface of the chest in the region of the head of the right clavicle. On percussion the right-sided aorta also produced a narrow band of dullness to the right of the sternum. In Cases 2 and 3 a pulsation was visible to the right of the sternum, in the second and third intercostal spaces.

CASE 4.—This patient, A. N., a forty-eight-year-old male, was examined on March 5, 1929. He was a stonecutter by occupation and had been engaged in this work for thirty-three years. The patient's chief complaint was marked shortness of breath which began in June, 1928. He continued to work until five weeks before examination. For the past six months the patient had had insomnia and orthopnea. There was dullness to the right of the sternum, with a visible pulsation in the second and third right interspaces. The aorta was palpable behind the head of the right clavicle. A definite tracheal tug was felt with the head elevated. The aortic second sound was heard best in the right supraclavicular fossa and in the first right intercostal space. Passage of a rigid stomach tube met with a resistance at the level of the third dorsal vertebra. At this point a distinct pulsation was transmitted along the tube to the finger tips. The tube could not be passed beyond this point since further pressure caused pain.

The fluoroscopic examination and photograph of the chest revealed normal apices. There was a marked increase in the lung markings around both hila due to passive congestion. In both lung fields there were numerous small irregular, sharply outlined spots. These were quite dense and were suggestive of a silicosis such as is seen in stonecutters. There was an obliteration of the right phrenicocostal angle by adhesions, with reduced mobility of the right diaphragm. The entire left phrenicocostal angle was occupied by a homogeneous dense shadow which extended upward over the apex of the heart. This shadow made it impossible to outline the apical region of the heart. The shadow was most likely due to thick pleural adhesions. (The patient had a severe attack of pneumonia with pleurisy nine years before, when he was sick for four months.)

The examination revealed an enlarged heart of aortic configuration. There was also enlargement of the heart to the right. Above the heart and to the right of the sternum was found the characteristic shadow of the ascending aorta. The shadow ran upward from the fourth intercostal space to the upper margin of the head of the right clavicle, where it curved to the left and again became visible behind the head of the left clavicle (Fig. 13). Here was seen, instead of a normal aortic knob, a small portion of the descending aorta running downward into the heart shadow. On account of a marked arteriosclerosis, the entire aorta was very distinctly visible. On posteroanterior fluoroscopy there was again the slight displacement of the trachea to the left at the level of the aortic arch. In fact, it was

this displacement of the trachea to the left which first attracted our attention. With barium paste we found the characteristic displacement of the esophagus in a curve to the left, visible on posteroanterior examination (Fig. 13).

In the first oblique position we found the identical picture of a retrotracheal and retroesophageal aortic knob such as we have already described in detail. The esophagus showed the anticipated semicircular forward displacement produced by the arch of the aorta (Figs. 14 and 15). We had again the characteristic picture of a persistence of the right aortic arch which takes its course behind the trachea and



Fig. 13.—Case 4. Showing the ascending aorta running upward on the right side above the level of the right clavicle. The esophagus is markedly displaced in a circle to the left. The descending aorta is just visible to the left of the esophagus. The heart is normal.

esophagus to reach the left side. The patient's clinical symptoms were due to cardiac decompensation, the result of marked silicosis, obliterative bilateral fibrous pleuritis, and emphysema. The aortic anomaly was an incidental finding as a result of the study of the previous three cases.

CASE 5.—This patient, Miss M. B., was seen by the writer on Nov. 23, 1931. She was then 24 years old. The patient had a severe cold, with symptoms of acute bronchitis which caused her to consult a physician. The patient had lived for one

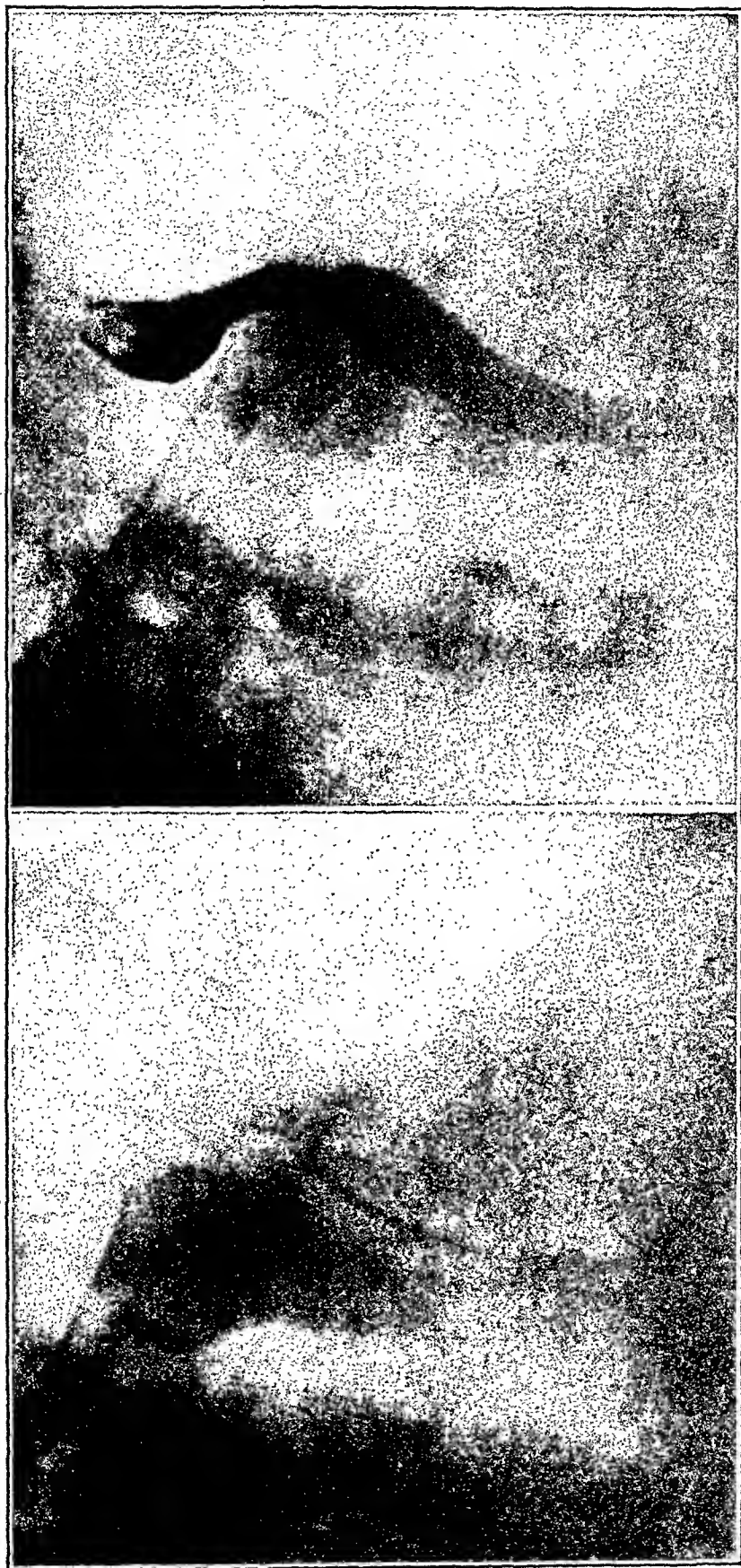


Fig. 15.

Fig. 14.

Fig. 14.—Case 4. The first oblique position. The aortic arch lies behind the trachea, which is markedly displaced forward and to the left.

Fig. 15.—Case 4. The first oblique position, showing the esophagus filled with barium. Here the characteristic displacement is clearly demonstrated, with the aortic arch behind the esophagus and trachea.

week, in August, with a young woman who developed active pulmonary tuberculosis, and she feared infection. There was no history of pleuritis, or hemoptysis. The patient had always been well. There was no evidence of cardiac disease. The patient was normally developed. The Wassermann test was negative.

On physical examination I was attracted by finding a slight pulsation in the second and third right interspaces and a loud aortic second sound in the first right intercostal space, and even louder in the right supraclavicular fossa. There were no murmurs. A pulsation could be felt on deep pressure in the fossa. The trachea deviated slightly to the left. There was also a definite tracheal tug with the head extended. I suspected a right-sided retroesophageal aorta, and fluoroscoped the patient.

The findings were the same as those observed in the other four cases. The ascending aorta arose from the right heart border at the level of the third right interspace and extended upward 1 inch to the right of the right vertebral border. It described a convex curve to the right upward to a point 1 cm. above the upper border of the right clavicle. Here it made a sharp curve to the left with displacement of the trachea and esophagus to the left (Fig. 16). No aortic knob was visible on the left side, and the naked pulmonary curve formed the first convex curve of the left heart border. The heart was of normal size.

The oblique positions showed the characteristic displacement of the esophagus and the trachea, with the pulsating retroesophageal aortic arch. The electrocardiogram was normal.

Of interest were the clinical findings of a visible pulsation in the second and third right interspaces, a palpable aortic pulsation in the right supraclavicular fossa, maximum intensity of the aortic second sound in the right supraclavicular fossa, slight displacement of the trachea to the left, and a tracheal tug.

CASE 6.—This case is of interest because the diagnosis was made by the writer from the physical examination and was confirmed by x-ray examination and necropsy. We shall see that in this case the complete anatomical diagnosis of persistent right aortic arch behind the trachea and esophagus, with persistent left aortic arch in front of the trachea (consisting of the left subclavian artery, isthmus stenosis, and diverticulum or left descending dorsal aortic root), was made and was confirmed.

The patient, a white male, forty-six years old, entered the Cook County Hospital, Chicago, on the writer's service on April 6, 1932. The chief symptoms were vomiting immediately after swallowing solid food, weakness, loss of weight, and melena for about six months. The difficulty in swallowing followed upon the extraction of all his teeth. There was some epigastric discomfort but no pain.

The past history revealed a chancre at 18, with a four-plus Wassermann reaction on several recent examinations. He had a very severe attack of typhoid at the age of 20. A herniotomy had been performed five years before. He had had large varices of both legs for several years, with varicose ulcers of the left leg.

Of special interest to us at this time were the chest findings. We shall omit a description of the other conditions observed. There was a slight tracheal tug. The trachea was displaced about $\frac{1}{2}$ inch to the left. There was a visible pulsation in the right first and second intercostal spaces. There was a visible and palpable pulsation in the right supraclavicular fossa, where a strong pulsation was easily felt on deep pressure. The aortic second sound was loud and ringing and heard best in the right first interspace and supraclavicular fossa. There was an area of dullness to the right of the sternum which extended upward to the right clavicle; it extended about 1 inch to the right of the sternum. There were no murmurs.

The heart was slightly enlarged to the left; the apex beat was in the fifth interspace in the midclavicular line. The transverse diameter was $5\frac{1}{2}$ inches. The Wassermann reaction of the blood was four-plus. There was a secondary

anemia, and the feces were positive for blood. On passage of a stomach tube, an obstruction was met at the level of the third dorsal vertebra, and *a definite pulsation was transmitted along the rigid stomach tube*. The tube could be passed beyond this obstruction but met a second impassable obstruction at the cardiac orifice. (The patient had a carcinoma of the cardia of the stomach.)

The blood pressure was 196 systolic, 122 diastolic in the right arm, and 190 systolic, with 110 diastolic in the left arm. The electrocardiogram was normal.

The clinical diagnosis was: (1) double aortic arch, with persistent right arch over the right bronchus and behind the esophagus, and left arch with an isthmus

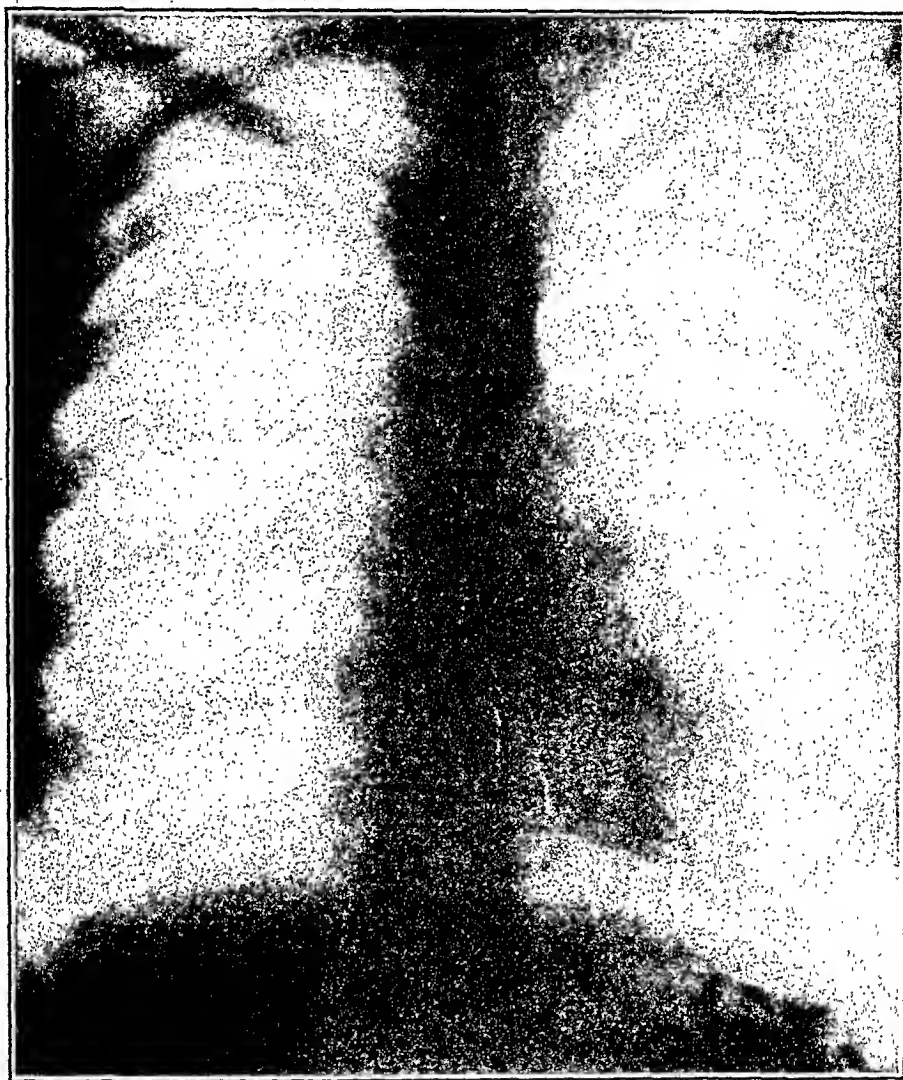


Fig. 16.—Case 5. A young woman twenty-four years old. The ascending aorta describes a convex curve to the right of the sternum, running upward above the right clavicle. The esophagus is displaced to the left, also the trachea. The descending arch is not visible. The heart is normal.

stenosis as described by the writer in Case 1 in August, 1925, and confirmed at autopsy. Furthermore, the other clinical findings not recorded in this paper added the following: (2) carcinoma of the cardia of stomach with liver metastases, (3) posttyphoid obliterative thrombophlebitis of both common iliac veins with collateral circulation, (4) syphilitic aortitis, (5) syphilitic endarteritis of cerebral arteries with areas of encephalomalacia.

The fluoroscopic examination of the chest presented a picture now very familiar to the writer, but one which could be easily overlooked.

The heart presented a normal appearance. Rising from the right heart border, at the level of the fourth right intercostal space, was a slightly convex shadow which extended upward to the right clavicle 1 inch to the right of the sternoclavicular joint. The shadow had a systolic pulsation synchronous with the heartbeat. The shadow formed a convex curve and ran across the vertebral column at the level of the third dorsal vertebra to reach the left side. It then ran downward from a point at the lower border of the head of the left clavicle in a convex curve to the left until it reached the left heart border in the third left intercostal space (Fig. 17). The trachea was displaced about $\frac{1}{2}$ inch to the left of the median line. To the left of the trachea at the level of the fourth dorsal vertebra there was a more dense semicircular shadow in the shadow of the aortic arch.

The posteroanterior view (Fig. 17) differs from the pictures in the other five cases only in the more conspicuous shadow of the descending portion of the aortic arch and descending thoracic aorta. It will also be noted that the descending aortic border has a wavy outline. Second, a round, more dense shadow is easily seen to the left of the trachea in the beginning portion of the descending arch. The more prominent descending aorta with its slightly wavy outline was interpreted as due to a syphilitic aortitis, and the round, denser shadow was considered to be the diverticulum, or descending dorsal aortic root. The diagnosis of double aortic arch was made and proved by the oblique views and examination of the esophagus. Already in the posteroanterior view the characteristic displacement of the esophagus in a circular curve to the left at the level of the arch may be seen. In the present case the esophagus was displaced 1 inch to the left by the retroesophageal right aortic arch.

The first oblique position showed clearly the large retroesophageal aortic knob (right aortic arch) and a second much smaller knoblike shadow in front of the trachea. Between these two lay the esophagus and trachea (Fig. 18).

In the second oblique position the entire ascending aorta was visible to the right of the trachea, which is partly obscured 1 inch above its bifurcation by the arch where it lies behind the trachea. At this same level the esophagus and trachea describe a curve anteriorly, due to the arch which runs around to the left side of both.

Here again we have conclusive proof of the presence of a persistent right aortic arch which runs over the right bronchus, then behind the trachea and esophagus. Furthermore, we have evidence of the existence of a diverticulum of the descending arch and of a left aortic arch as well.

The diagnosis which was made on April 20, 1932 was: total persistence of the right aortic arch with retroesophageal course, persistence of the left aortic arch in the form of a left subclavian artery, isthmus stenosis, and diverticulum or left descending dorsal aortic root; syphilitic aortitis, with widening of the aorta.

The patient died on June 17, 1932, from a severe hemorrhage of the stomach resulting from the carcinoma of the cardiac portion. The autopsy was performed by Dr. R. H. Jaffe, director of the Pathologic Institute. Only those findings which concern the heart and aorta will be given at this time.

The heart weighed 275 gm. The left ventricle was 18 mm., the right, 3 mm. thick. The myocardium was grayish brown and friable. *There were no anomalies in the heart.* The valves appeared normal.

The ascending aorta ran upward on the right side, in the direction of the head of the right clavicle. It made a slight convex curve to the right. It ran over the right main bronchus and behind the trachea and esophagus until it reached the left side. Its transverse diameter was 28 mm. Eight centimeters above the aortic valve it gave off its first large branch, the left innominate artery. This artery was 11 mm. in diameter and divided 20 mm. from its origin into the left carotid and the left subclavian artery. The left innominate and its bifurcation lay directly in

front of the trachea and 20 mm. above the bifurcation of the trachea. The left common carotid measured 7 mm. in diameter, the left subclavian 9 mm. (Figs. 19 and 20).

Forty millimeters from the origin of the left innominate and 20 mm. from the origin of the subclavian artery, the latter artery formed an angle of about 135

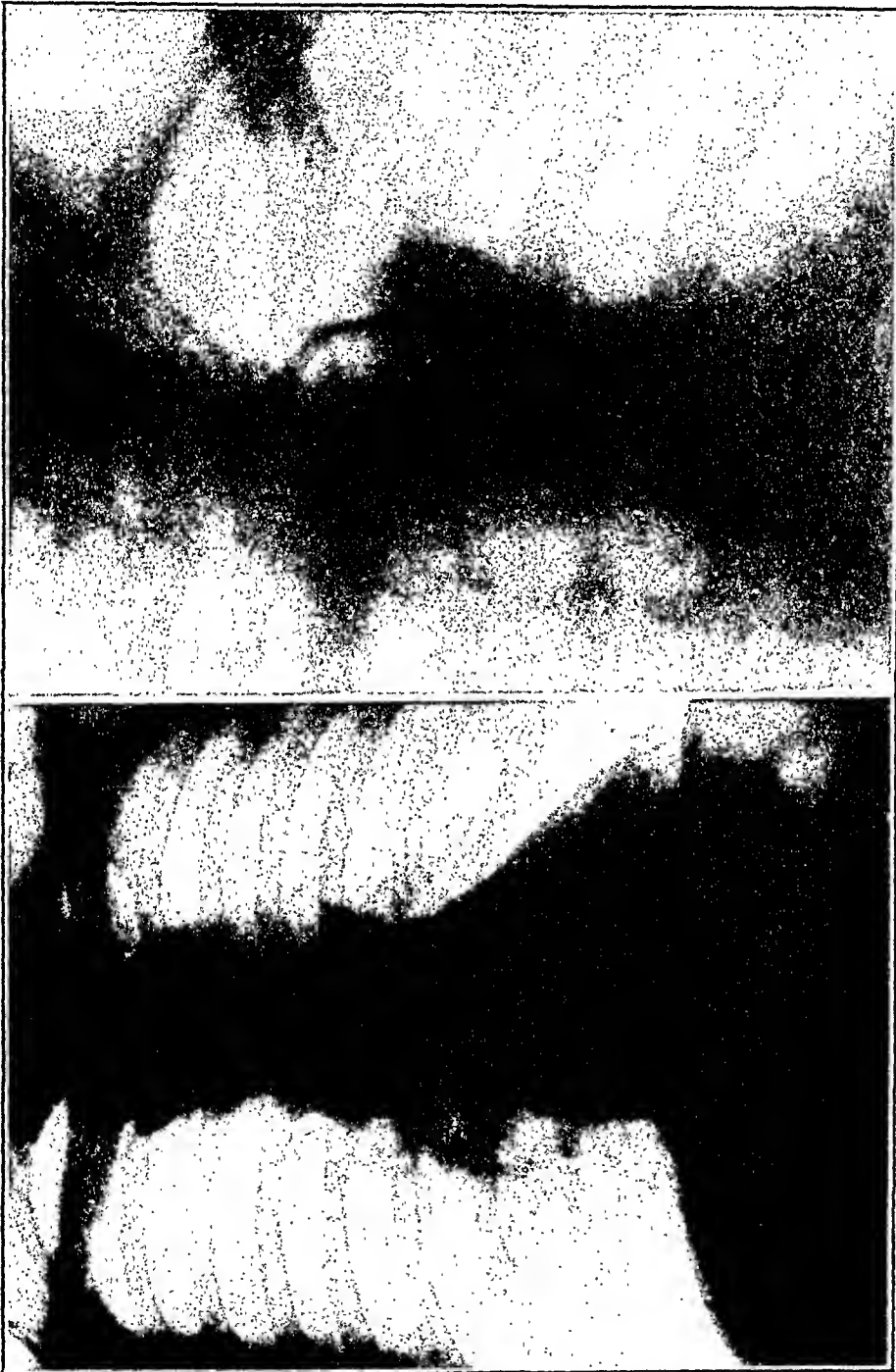


Fig. 18.

Fig. 17.

Fig. 17.—Case 6. Double aortic arch of the same type as the other five cases. This case is the second confirmed at autopsy by the writer. Here the ascending aorta is visible on the right side, and the descending aorta on the left side. The trachea is displaced to the left and compressed. In the descending arch, just below the head of the left clavicle, the shadow of the aortic diverticulum (left descending dorsal root) is distinctly visible. The heart is normal.

Fig. 18.—Case 6. The first oblique position. The esophagus contains barium. Note the wide syphilitic nortle arch behind the esophagus. There is a second smaller arch in front of the esophagus. The latter represents the left innominate and subclavian artery forming part of the left fourth arch.

degrees and ran upward along the left border of the trachea. Attached to the point of angulation was a stenosed vessel 4 mm. in diameter and 9 mm. in length. This vessel united the left subclavian artery with a diverticulum-like pouch in the anterior wall of the retroesophageal aortic arch. This pouch lay along the left border of the esophagus, and together with the arch, displaced the esophagus anteriorly in the form of a semicircle. The pouch also displaced the left border of

the esophagus in a slight curve to the right. The pouch or diverticulum was dome shaped and 25 mm. in diameter at its origin. It projected 15 mm. beyond the anterior surface of the descending arch of the aorta.

Running from this diverticulum (left descending dorsal aortic root) was a second vessel, the ductus Botalli, which ran downward and to the right to reach the pulmonary artery. It was 40 mm. long and 3 mm. in diameter. Its lumen was obliterated. It lay in front of the left main bronchus.

Two centimeters above the origin of the left innominate artery the arch gave off its second branch, the right common carotid artery. This artery was 8 mm. in diameter and lay to the right of the trachea, originating from the aortic arch

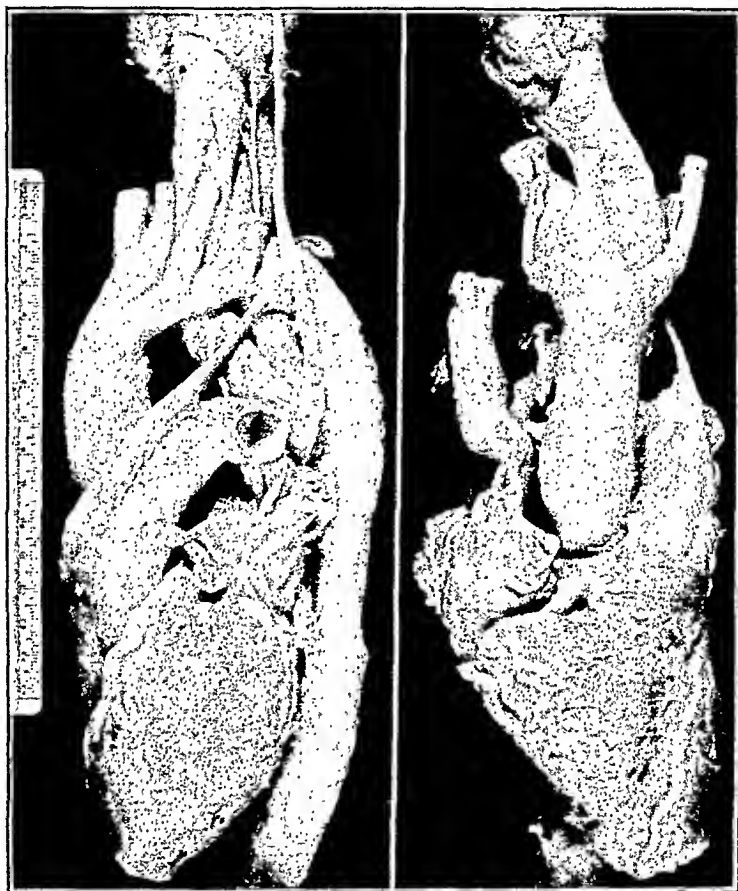


Fig. 19.

Fig. 20.

Fig. 19.—Photograph of the heart and vessels in Case 6, after dissection by the writer. Note the double aortic arch described under Case 6. The right arch lies behind the trachea and esophagus, and the left arch (left innominate and subclavian artery, isthmus stenosis, and left dorsal root) in front. The ductus arteriosus communicates with the left dorsal root.

Fig. 20.—Specimen in Case 6, viewed from the right side showing the aortic arch behind the trachea and esophagus, with the left arch in front.

where it lay above the right main bronchus. The aortic arch then ran behind the trachea and esophagus, displacing both to the left and especially anteriorly. The right bronchus was displaced slightly posteriorly by the aortic arch, which rested upon it. The third branch of the aorta was the right subclavian artery which originated 15 mm. above the right carotid. It measured 10 mm. in diameter and lay directly behind the trachea in contact with the right border of the esophagus.

The right recurrent laryngeal nerve ran under the right retroesophageal aorta directly below the right subclavian artery. The left recurrent laryngeal nerve

originated in front of the aortic pouch, and ran beneath and behind it at the attachment of the stenosed isthmus and the ductus Botalli.

After giving off the right subclavian artery the right aortic arch proceeded in a convex curve upward and to the left behind the trachea and esophagus (Fig. 20). It displaced both as already described. It formed a deep bed in the right and posterior wall of the esophagus. Three centimeters to the left of the right subclavian the arch gave off the diverticulum. This pouch, therefore, lay to the left of the spine and to the left of the esophagus. The descending portion of the arch and the thoracic aorta formed a curve around the esophagus and came to lie in contact with the left border of the esophagus. The aorta varied in its caliber in different portions, suggesting syphilitic aortitis. The lower half of the abdominal aorta was firmly attached to the anterior aspect of the spine by a very firm grayish white tumor tissue. The periaortic lymph nodes were infiltrated with tumor tissue.

THE EMBRYOLOGICAL DEVELOPMENT OF THIS ANOMALY

The embryological development of these cases of persistence of the right aortic arch associated with partial occlusion of the left is illustrated

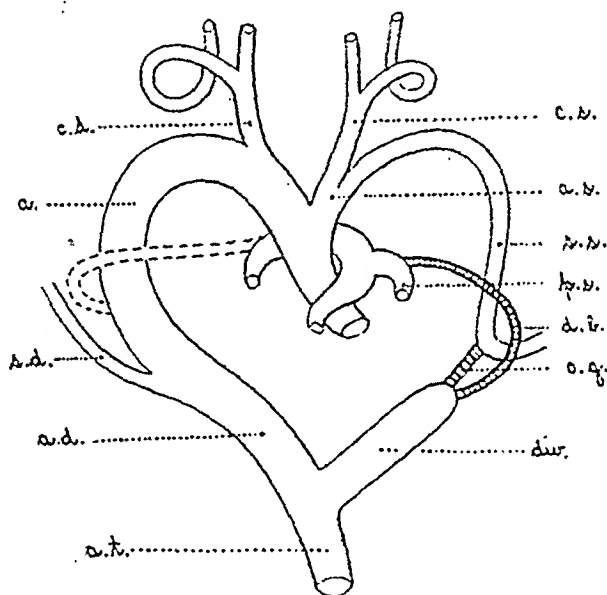


Fig. 21.—Diagram which explains the embryonal development of Cases 1 to 6 inclusive, of total persistence of the right aortic arch and isthmus stenosis of the left aortic arch. The aorta arises from the right fourth arch, the left subclavian and occluded vessel from the left fourth arch. The diverticulum represents the left descending dorsal aortic root.

c.d., right carotid
a., aorta
s.d., right subclavian
a.d., descending aorta
a.t., thoracic aorta
o.g., occluded vessel

c.s., left carotid
a.s., left innominate
s.s., left subclavian
p.s., left pulmonary
d.b., ductus Botalli
div., diverticulum.

in Fig. 21. The right fourth branchial artery together with the right descending dorsal aortic root have formed the aorta, instead of the left. The left fourth arch has developed into the short left innominate artery and the left subclavian so that these are now the first branch of the right-sided aorta. The craniad persisting part of the ascending aorta and the third arch form the carotids on both sides, on the left going off from the left innominate and on the right forming the second branch of the aorta. The right subclavian forms the third branch of the aorta.

Of special interest in our case is the persistence of the left fourth aortic arch as the left subelavian artery and the lateral communicating branch between the fourth arch and the left aortic root (short occluded vessel between the left subelavian and the diverticulum). The diverticulum represents the left descending dorsal aortic root, to which the ductus Botalli is attached. This explanation of the development of our cases makes clear the anatomical and roentgenological findings. The course of the right-sided aorta behind the trachea and esophagus is due to the persistence of the left fourth aortic arch, which forms a tight ring around the trachea and esophagus. The presence of the occluded vessel between the left subelavian artery and the diverticulum causes the aorta to be located to the left and behind the trachea and esophagus instead of on the right side. We really have a condition similar to that found in persistence of both aortic arches, a right totally persistent posterior arch, and a left partially occluded anterior arch (subelavian artery, short occluded vessel and diverticulum).

As in almost all cases of persistence of the right aortic arch, so also, in these cases, the left ductus Botalli persists. The ductus Botalli, which must maintain its communication between the pulmonary artery and aorta during fetal life, holds firmly to its attachment to the aorta, in our cases to the left descending dorsal root. We may look upon this anomaly as an isthmus stenosis of the left fourth arch if we wish to call the occluded vessel or cord between the left subelavian artery and the diverticulum the isthmus of the aorta. Had the left fourth arch not persisted we would have had cases similar to the right-sided aorta with right-sided arch (Fig. 4). Such anatomical specimens have been reported by Versari, Reid, Hoepke, Stibbe, Jaffe, Pense, and others. There is a tendency of a right-sided aorta to remain on the right side, due perhaps to hydromechanical factors, unless the left fourth arch persists and pulls the aorta behind the trachea and esophagus. The embryological development of our cases will be even more clearly visualized by the study of the model of the aortic arches from a human embryo 12.5 mm. long, which Prof. Hoehstetter, of Vienna, kindly permitted the writer to reproduce here (Fig. 22).

Congdon has described similar findings in his study of the 13 mm. embryo. The ascending aorta divides into a right and left fourth arch, and the two dorsal aortic roots combine to form the descending thoracic aorta. The left sixth arch forms the ductus arteriosus. This condition of double aortic arch found in the 12 to 13 mm. embryo may persist to form the double aortic arch found after birth. The right arch, usually behind the esophagus and trachea, is often larger than the left arch in front of the trachea. Or, there may develop an isthmus stenosis of the left aortic arch during this early embryological development. In such a case the right aortic arch is forced to persist by the blood current con-

tinuing through the right arch. It is just this condition which I found and explained on an embryological basis in my first case in 1926.

That this explanation was correct has been recently confirmed in the findings at the autopsy of my sixth case, in which I was able to make a perfect anatomical diagnosis from the x-ray and clinical findings. A comparison of the specimens in my Cases 1 and 6 indicate that they represent the same anomaly, which I predicted in 1926 was not rare but had been overlooked.

Blackford two years later proved my contention that obliteration of the left fourth arch, resulting in persistence of the right aortic arch, is related embryologically to coarctation of the aorta of the infantile type. If the left fourth arch becomes stenosed or obliterated after the atrophy of the right fourth arch, then a coarctation of the aorta with its con-

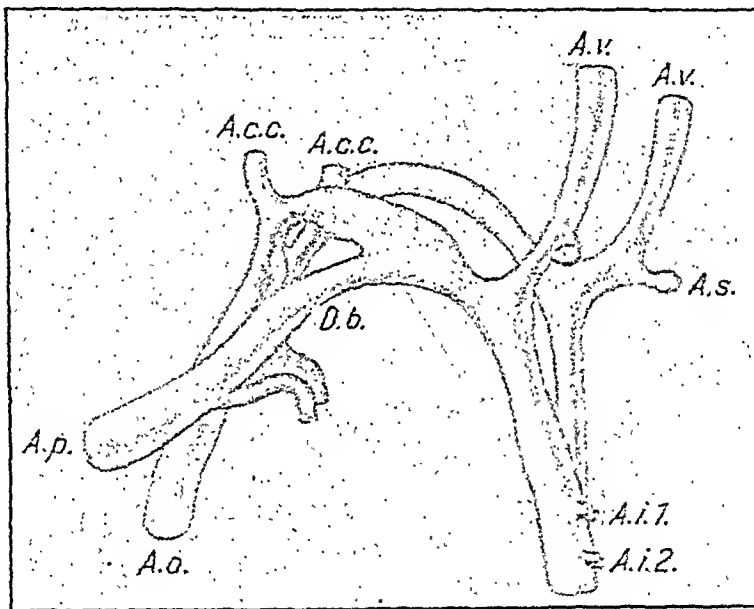


Fig. 22.—Drawing of the large vessels of a 12.5 mm. human embryo made by Professor F. Hochstetter (*Anat. Hefte*, Vol. 43). This model shows both aortic arches and the ductus Botalli. It is of great value in explaining our case. If the right arch persists and the communication between the left arch and left aortic root becomes occluded, then we have the anomaly described in Cases 1 and 6.

A.p., pulmonary artery
A.o., ascending aorta
D.b., ductus Botalli
A.c.c., common carotid

A.v., vertebral artery
A.s., subclavian artery
A.i.1., first intercostal
A.i.2., second intercostal.

sequent effect upon the heart and circulation must result. In the six cases which I have described, the right aortic arch therefore acts as a safety valve for a stenosis of the left arch in early fetal life. There results a persistence of both aortic arches as in reptiles. The right arch is usually of normal size and runs over the right bronchus and behind the trachea and esophagus; the left arch persists in the form of the left subclavian artery, stenosed vessel or isthmus stenosis, and the diverticulum of the descending thoracic aorta (left descending dorsal root).

In 1930 Sprong and Cutler collected 54 cases of right arch in the anatomical literature; of these 15 were cases of double aortic arch.

Roschdestwensky found 11 of which 3 were the same as Sprong and Cutler's, making 23 cases. Schleussing, Harris and Whitney, Roschdestwensky, Lockhard, Arkin (Case 6), and Snelling and Erb add 6 more cases, making a total of 29 studied anatomically. Arkin adds 4 cases studied clinically and roentgenologically, Blackford 1 case, and Biedermann, also Mardersteig, have reported cases diagnosed roentgenologically. It was Arkin's publication in 1926 which first made the diagnosis possible *intra vitam*. Blackford, Davenport and Bayley have recently gathered 66 cases of right aortic arch from the anatomical and pathological literature. They presented clinical and x-ray findings in a case in a ten-year-old child with a persistence of the right aortic arch accompanied in all probability by a patent ductus arteriosus and inter-ventricular septum defect. There was no autopsy.

It is difficult to explain the persistence of the right aortic arch instead of the normal left arch. We know that both arches are normally present in reptiles, the right arch in birds, and the left in mammals. Perhaps the direction of the blood current is the determining factor, and a slight change in the direction of the blood stream in early fetal life causes the stream to use the right arch more than the left. If that be the case, then we must assume that the direction of blood flow from the pulmonary artery does not change, for we almost always find a left-sided ductus Botalli in cases of right-sided aorta.

DISCUSSION

From the study of these six cases of persistent right aortic arch, as well as the literature on anomalies of the aorta and large arteries, I feel confident that it will be possible to diagnose roentgenologically, and perhaps clinically, still other anomalies.

For clinical and roentgenological purposes the anomalies of the aorta may be classified as follows:

1. *Double aortic arch* (persistence of the right and left aortic arches with patency of both arches).
2. *Right aorta with right-sided arch* (type first described by Assmann).
3. *Right aorta with retroesophageal arch* (type first described roentgenologically and the diagnosis confirmed by Arkin), usually associated with isthmus stenosis of left arch.
4. *Coarctation (isthmus stenosis) of the left aortic arch.*
5. *Absence of part or all of the left aortic arch.*

In *total persistence of both aortic arches* we may expect x-ray findings in the first oblique position resembling those described for right retroesophageal aorta. In addition, a second knob would be visible in front of the trachea. The esophagus would be compressed and displaced forward and to the left; the trachea would have in front of it the other arch. The left or anterior arch is usually smaller than the right: hence

we would expect to find the knob in front of the trachea to be the smaller of the two. They may, however, be of equal size. This anomaly should be easy to recognize since the picture is almost the same as in my six cases.

In *right aorta with right-sided arch*, in which the ascending aorta, arch, and a portion of the descending aorta are all on the right side, we must always look for a left descending aortic root behind the esophagus. This important fact was first emphasized by me in 1926 and recently was confirmed by Blackford, Davenport, and Bayley. This usually forms a diverticulum going off from the left wall of the right-sided descending arch of the aorta. This pouch, which gives off the left subclavian artery and also communicates with the ductus Botalli, produces a forward dislocation of the esophagus which should be easy to recognize in the oblique positions. The esophagus would most likely be dislocated forward, perhaps also to the left. The dislocation would usually be below the level of the aortic knob. A semicircular forward displacement of the esophagus below the level of the right arch would speak for the presence of the left dorsal aortic root behind the esophagus. The subclavian artery may also run behind the esophagus in such cases and could be distinguished by its smaller size. In rare cases, where the diverticulum is very short or absent, the ductus Botalli may be forced to run behind the esophagus to reach the right-sided aorta. In such an event the esophagus would be pushed forward on its left posterior border. It might even be displaced to the right and forward.

In right-sided aorta, or persistence of the right aortic arch, the esophagus may therefore be dislocated by (1) a right-sided aorta with retro-esophageal arch, as in my six cases; (2) a diverticulum formed from the left descending dorsal aortic root, as in the type first described by Assmann; (3) a left subclavian artery as the last branch of the right-sided arch; or (4) the ductus Botalli running behind the esophagus.

Another form of so-called dysphagia lusoria or arteria lusoria due to an anomalous right subclavian artery should be mentioned here. This is a type found in cases with a normal left-sided aortic arch. The right subclavian is the last large branch of the aortic arch and hence runs behind (rarely in front of) the esophagus to reach the right side.

In these cases the right subclavian artery may originate as a diverticulum or pouch which represents the right descending dorsal aortic root. This anomalous right subclavian stands in no relation to the ductus Botalli as does the left, hence the abnormal right subclavian has a more variable origin than the left. In 80 per cent of cases collected by Holzapfel the abnormal right subclavian ran behind the esophagus, in 15 per cent between trachea and esophagus, and in 5 per cent in front of the trachea. It is usually located at the level of the second to fourth thoracic vertebrae. X-ray examination of the esophagus should reveal such a vessel in some cases.

The above five types of esophageal displacement (so-called dysphagia lusoria) are of importance because they may cause a dysphagia. They should be of special interest to those who do bronchoscopy and esophagoscopy. The danger of such an examination in any of my six cases of retroesophageal aorta is obvious. It is certainly advisable always to order an x-ray examination of the chest, including the esophagus, before permitting such instrumentation. Of our six cases none had symptoms directly related to the anomalous aorta. The sixth patient had dysphagia, but it was due to a carcinoma of the cardia of the stomach and lower end of the esophagus.

I have discussed these anomalies of the aorta and great vessels in the hope that roentgenologists who have the opportunity of fluoroscoping large numbers of patients will keep them in mind and recognize such cases.

To the clinician I wish also to call attention to certain physical findings which should attract his attention enough to order an x-ray examination for my type of right retroesophageal aorta.

In the six cases I have found the following signs:

1. Dullness on percussion along the right sternal border upward to the head of the right clavicle.
2. Visible systolic pulsation in the second or third right intercostal space near the sternum, or in the right supraclavicular fossa.
3. Palpable strong pulsation in right supraclavicular fossa.
4. Maximum intensity of the aortic heart sounds to the right and above the usual location. (Often in the right supraclavicular fossa.)
5. Displacement of the trachea slightly to the left.
6. Tracheal tug.
7. Delay in the passage of a rigid stomach tube at the level of the third dorsal vertebra with pulsation transmitted along the tube.

It is not to be expected that all of these signs will be positive in every case. In my six cases the heart presented normal findings in all; there was no clinical or post-mortem evidence (in two cases) of cardiac anomalies. The electrocardiograms obtained in four of the cases were normal. Aortic anomalies frequently occur in the absence of cardiac malformations. Theoretically, accurate timing of the pulsation in the carotid and subclavian arteries should also be of value in the diagnosis of some of the anomalies we have discussed. For example, in my type of double aortic arch a left innominate usually forms the first large branch of the aorta, followed by the right carotid and right subclavian. In anomalous right subclavian artery arising from the descending aorta the pulsation in the subclavian should also be slightly delayed.

CONCLUSIONS

Six cases of a clinically new aortic anomaly are presented, two with post-mortem findings. This consists of a total persistence of the right

aortic arch, combined with a persistence of the left aortic arch in the form of the left subclavian artery, an isthmus stenosis, and a diverticulum of the aortic arch (left descending dorsal aortic root). In other words, we have here a persistence of both aortic arches as in reptiles. The right arch lies behind the esophagus, and the left arch in front of the trachea.

The cases all present characteristic x-ray findings which are: (1) a shadow to the right of the sternum, running upward to the head of the right clavicle, with a distinct systolic pulsation; (2) slight displacement of the trachea, and definite displacement of the esophagus to the left; (3) absence of the normal aortic knob on the left side, or only a small shadow of the descending arch on the left side; in some cases two aortic knobs, one on each side; (4) in the right oblique position the aortic knob lies behind the trachea and esophagus, both of which are displaced forward and to the left (most characteristic of all is the circular forward displacement of the esophagus by the arch of the aorta); (5) shadow of the diverticulum either in the retroesophageal knob or in the shadow of the descending arch on the left side; (6) in the left oblique position a wide shadow of the ascending aorta to the right of the trachea and evidence that the aortic arch runs behind the esophagus to reach the left side.

The first case was diagnosed in 1925 and confirmed at autopsy. Since that time five additional cases have been diagnosed and are described. The last case was recognized clinically and the diagnosis confirmed by x-ray examination and autopsy. In this case a complete anatomical diagnosis was made with the aid of the roentgen ray.

The following clinical signs were found in the six cases: (1) dullness to the right of the sternum, (2) visible systolic pulsation in the second and third right intercostal spaces, (3) palpable, strong pulsation in the right supraclavicular fossa, (4) maximum intensity of the aortic sounds in the region of the head of the right clavicle, (5) slight displacement of the trachea to the left, (6) tracheal tug, (7) delay in passage of the stomach tube at the level of the third dorsal vertebra, with transmitted pulsation from the arch of the aorta.

Attention is called to the presence of aortic anomalies without any cardiac malformations and in many cases without clinical symptoms. The embryological development and clinical significance of this new clinical and x-ray picture are discussed. Suggestions are given for the recognition of still other anomalies of the aorta and its large branches. The great importance of examination of the esophagus in anomalies of the aorta is stressed.

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THE VELOCITY OF THE BLOOD FLOW IN THERAPEUTIC HYPERPYREXIA*

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IT IS the purpose of this communication to report the results of a study of the effect of artificial fever produced by diathermy, electric blanket, and typhoid vaccine upon the velocity of blood flow as determined by the decholin method in two patients, one with an apparently normal heart, and the second with syphilitic heart disease. Treatment of patients with general paresis by these means afforded the opportunity for these studies.

Various observers^{1, 2, 3} have already shown that in exercise and hyperthyroidism, with an increase in the body metabolism, an increase in the velocity of the blood flow occurs. Kissin and Bierman⁴ have recently shown that therapeutic fever produced by the radiotherm likewise causes an increase in the velocity of the blood flow. It was felt that repeated determinations of the velocity of the blood flow on the same patient as fever therapy continued might be of interest, enabling one to note (a) residual effects if any upon the basal velocity of blood flow and (b) the velocity of flow for different temperature levels.

Subjects.—Observations were made upon two patients: Patient 1, S. C., aged thirty-two years; height 67 inches; weight 120-125 pounds. Diagnosis: General paresis. There were no signs or symptoms of cardiac pathology. Patient 2, M. M., aged forty-four years; height 67 inches; weight 164-170 pounds. Diagnosis: General paresis, syphilitic heart disease with cardiac hypertrophy and aortic insufficiency, and hematuria of unknown origin. There were no signs or symptoms of cardiac decompensation.

Methods.—The method of Winternitz⁵ as modified by Gargill² was used to determine the arm-to-tongue velocity flow. From 3 to 4 c.c. of 20 per cent decholin (sodium dehydrocholate) solution were injected into the median cubital vein as rapidly as possible (usually within less than one second), the duration of the injection being noted with a stop watch. The time elapsing from the end of the injection to the onset of a bitter taste was also noted and considered the "real arm-to-tongue time."² The pathway traversed by the decholin is as follows: from the right elbow to the right side of the heart, to the lungs, the left side of the heart, the internal carotid artery and then to the tongue.

The method of inducing hyperpyrexia by means of diathermy has been described by others.⁶ In this clinic, however, segmented electrodes encircling the waist, the upper arms, and the thighs are used and are applied with care not to cause any vascular constriction. The right arm electrode was loosened before each injection of decholin. As insulating covering, a large celotex box containing eight 60-watt

*From the Neurosyphilis Clinic of the Boston Psychopathic Hospital under the direction of Dr. Harry G. Solomon, Chief of Therapeutic Research.

electric bulbs completely encloses the patient (with the exception of the head). The patient's movements are relatively unrestricted. Three doors in the box permit manipulations of the patient. The dry and wet bulb temperatures of the air blanket within the insulating box rise rapidly as treatment continues, and, since very little circulation of air occurs, air blankets of different temperatures are present as one proceeds from body level to the roof of the box. Dry and wet bulb levels of about 105° and 120° F., respectively, are obtained in about one hour, fifteen inches above body level.

Fever induction by means of the electric blanket did not differ from the method described by Wilgus and Lurie.⁷ Typhoid vaccine fever was induced by the intravenous injection of from 125 to 1,250 million bacteria.

Patient S. C. received five diathermy treatments, six electric blanket treatments, and three intravenous typhoid vaccine shocks, totaling fourteen fever treatments over a period of four weeks. Patient M. M. was given eleven diathermy treatments over a period of six weeks.

In each instance observations were made on the patient under basal conditions before fever was induced. Following a period of from twenty to forty minutes during which the pulse rate and blood pressure were observed every five minutes, a single observation of the blood velocity and occasionally a second determination was made. The duplicate determinations invariably checked within two seconds. These values for blood velocity flow and average values of the blood pressure levels and of the pulse rates during the rest period were used as basal values for the experiment. Fever treatment was then started and velocity rates determined with temperature rising, at a stationary level, and falling. Rates were obtained during the typhoid chill. Pulse rates were counted for twenty to thirty seconds during the velocity determinations. Blood pressures were taken immediately before or after, and body temperature at the time of the test. Rectal temperatures, recorded by means of a self-recording Leeds-Northrup temperature unit inserted during the entire treatment, were used in all experiments except in the electric blanket treatment. In the latter experiments mouth temperatures were used since only slight differences have been found between oral and rectal readings in this type of fever.

RESULTS

Basal Velocity Rates.—Sixteen basal velocity determinations were obtained on S. C., whose heart was normal to examination before the induction of fever on fourteen treatment days (Fig. 1). The basal arm-to-tongue velocity rates varied from 18 to 9.5 seconds and tended to increase during the later days of the fever treatments. The changes in the velocity of the blood flow were accompanied by parallel changes in other clinical findings, the basal pulse rate varying from 56 to 80 per minute, the body temperature from 96.7° to 99.3°, the diastolic pressure from 47 to 63 mm. mercury, the systolic pressure from 82 to 98 mm. mercury, and the pulse pressure from 30 to 41 mm. mercury.

Eleven basal velocity rates were obtained on M. M., who showed evidences of latent heart disease, on eleven treatment days and ranged from 20.2 to 14.6 seconds (Fig. 2). The velocity rates of this patient also tended to increase as fever therapy continued but were accompanied by changes in other clinical findings which did not parallel

the changes in the basal velocity of the blood flow. The basal pulse rate was slowed as fever therapy was repeated, ranging from 83 to 58 per minute; the body temperature varied from 96.5° to 98.8° ; the

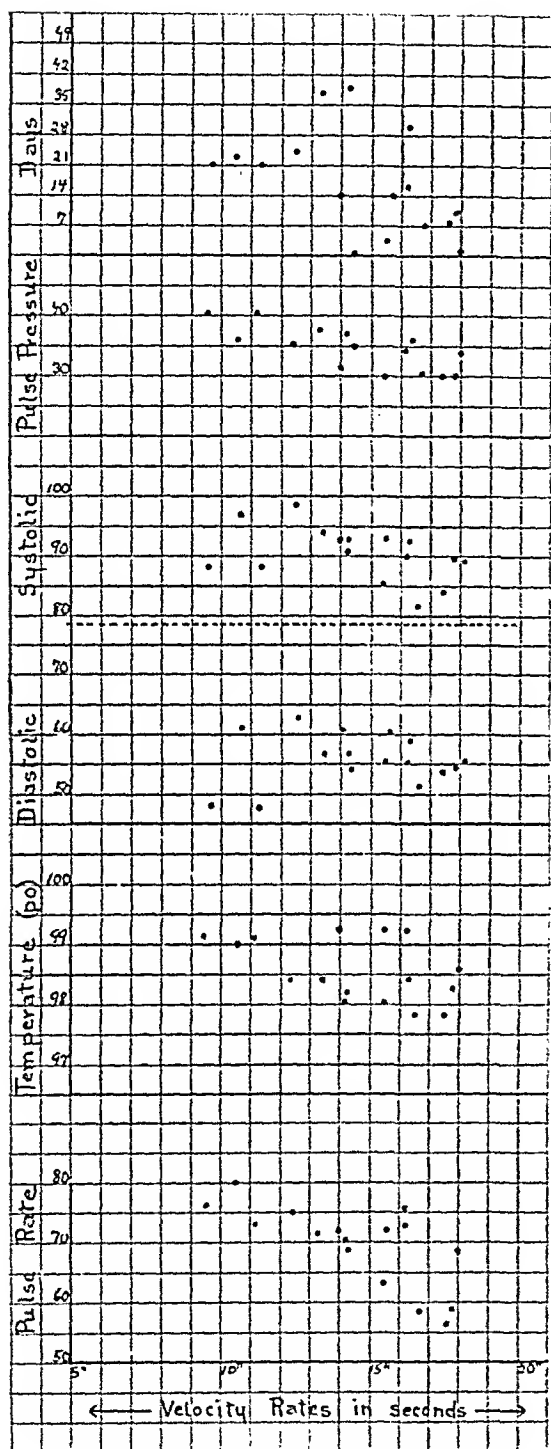


Fig. 1.

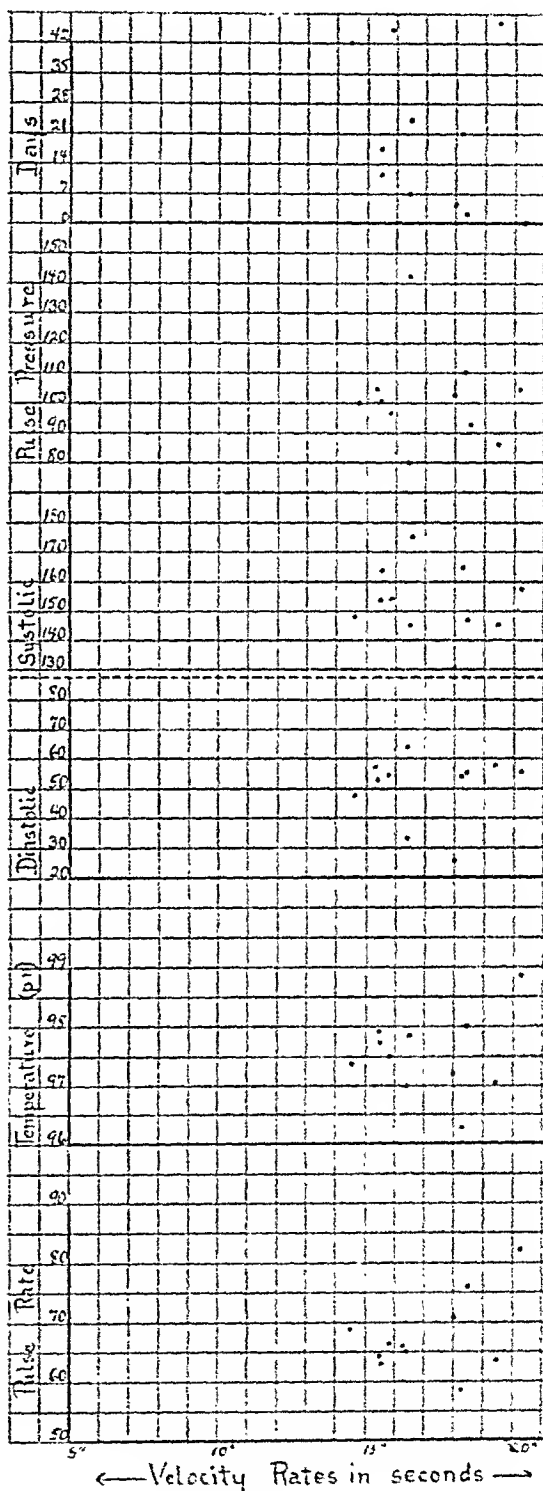


Fig. 2.

Fig. 1.—Velocity rates under basal conditions (Patient S. C.).

Fig. 2.—Velocity rates under basal conditions (Patient M. M.).

diastolic pressure, from 25 to 65 mm. mercury; the systolic pressure, from 130 to 175 mm. mercury, and the pulse pressure, from 80 to 143 mm. mercury.

A comparison of the basal velocity rates obtained on both patients reveals more marked changes in those of the patient with an apparently normal heart, S. C. In both patients a hastening of the basal

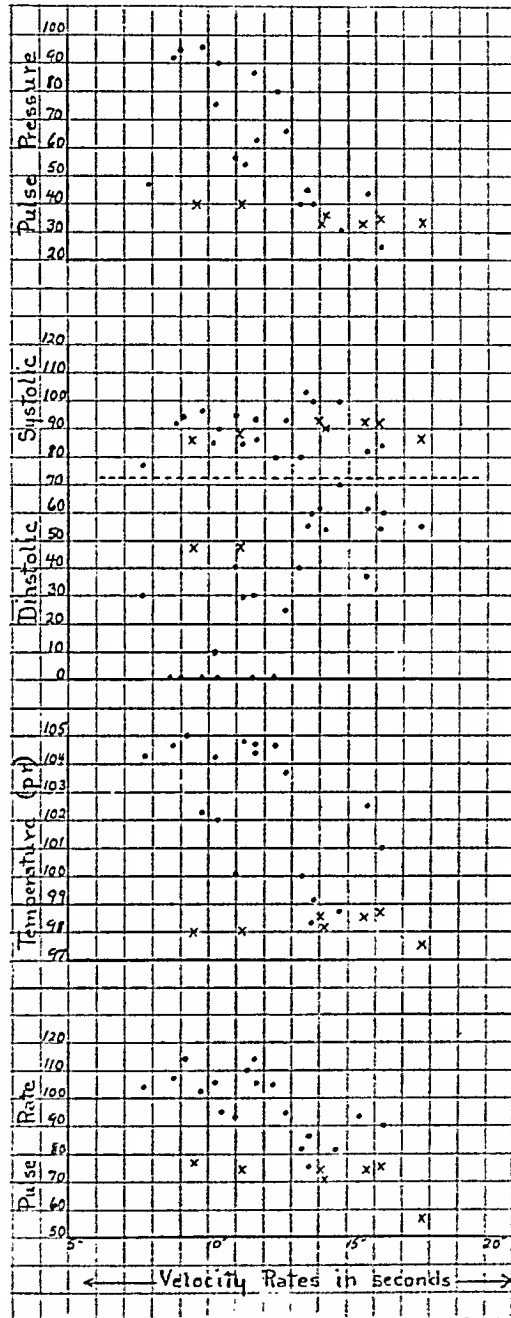


Fig. 3.—Velocity rates in fever produced by diathermy (Patient S. C.). "X" equals basal rates included for comparison.

flow occurred as fever therapy continued, accompanied by an increase in the pulse rate of S. C., but by a slowing of the pulse rate of the patient with luetie heart disease. The basal velocity rates of S. C. show a linear relationship best to the pulse rate; those of M. M. also to the pulse rate, but an inverse one.

Velocity Rates During Fever.—During the induced fevers fifty arm-to-tongue velocity determinations were obtained on S. C. and consisted of the following: 18, 17, and 15 determinations during diathermy,

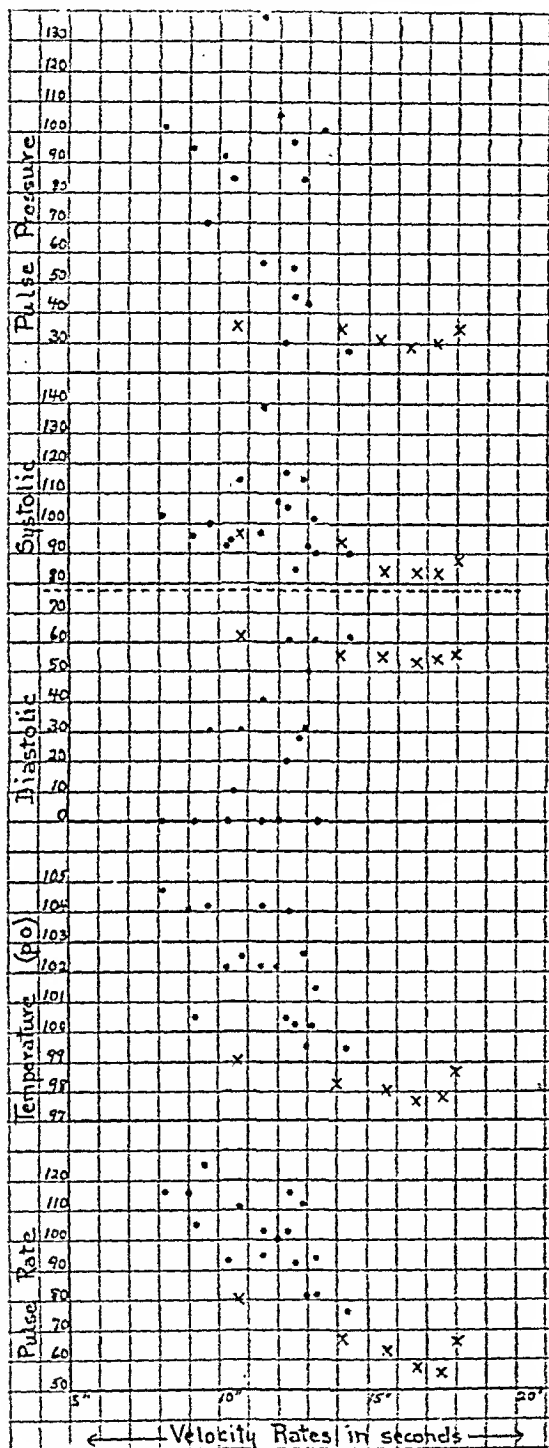


Fig. 4.

Fig. 4.—Velocity rates in fever produced by electric blanket (Patient S. C.). "X" equals basal rates included for comparison.

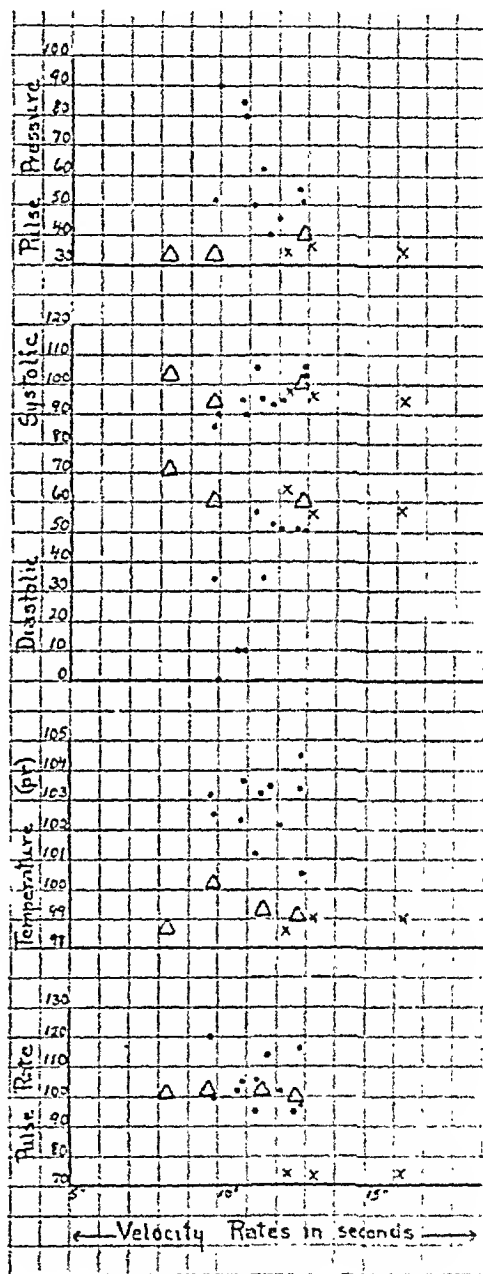


Fig. 5.

Fig. 5.—Velocity rates in fever produced by protein shock (typhoid) (Patient S. C.). "X" equals basal rates; Δ, chills.

electric blanket therapy, and typhoid vaccine fever, respectively (Figs. 3, 4, and 5). An increase in the velocity of flow occurred at

all times, with but one exception, as body temperature was rising. With a fall in body temperature the velocity of flow was less rapid than at a similar level when body temperature was rising, on some occasions slower than the basal level obtained before fever therapy was started even though body temperature was four degrees above the basal level. Variations in the velocity rates of six seconds were present for similar pulse and temperature levels. No absolute relationship could be found between the percentage increases in the velocity of blood flow and other clinical findings. During diathermy fever, however, a suggestive linear relationship is best seen between the velocity of the blood flow and the pulse rate, less so between the velocity of flow and the pulse pressure. In fever induced by the electric blanket, a similar relationship is apparent between the velocity of flow and the pulse level, less so between velocity of flow and the body temperature. The determinations obtained during typhoid vaccine fever show less variation, and the percentage increases in the velocity of flow are less marked for equal rises of body temperature than occur during diathermy and electric blanket fever. The changes in other clinical findings such as systolic, diastolic, and pulse pressures and pulse rate are also less marked for this type of induced fever.

The four velocity rates obtained on S. C., during the chill following the intravenous injection of typhoid vaccine are of considerable interest. Table I shows the percentage deviations from basal conditions occurring at this time. The pulse rate is increased from 33 to 41 per cent. The velocity of the blood flow, however, increased from 6 to 50 per cent above basal conditions. The percentage deviations of the velocity of flow and of pulse rate do not run exactly parallel but do show a closer relationship than that found between the velocity of flow and other clinical findings.

Twenty velocity determinations were obtained on M. M. during diathermy fever (Fig. 6). An increase in the velocity of blood flow

TABLE I
DEVIATIONS FROM BASAL CONDITIONS DURING TYPHOID VACCINE CHILL

	EXPERIMENT I		EXPERIMENT II	
	OBSERVATIONS			
	I	II	I	II
Velocity rate	50%	6%	4%	28%
Pulse rate	33%	35%	39%	41%
Pulse pressure	0	—*	2%	—12%
Systolic pressure	6%	—	4%	— 2%
Diastolic pressure	9%	—	5%	5%
Body temperature (p.o.)	0.2° F.	—	0	2° F.
Body temperature (p.r.)	0.1° F.	0.5° F.	0.1° F.	1.2° F.

*No observations made.

occurred always when body temperature was above basal level with but one exception—when the body temperature was falling. The results obtained reveal also less marked increases as the body temperature was falling than when rising and bore no absolute relationship to other clinical findings. Variations in the velocity time of as much as seven seconds were obtained for similar temperature levels.

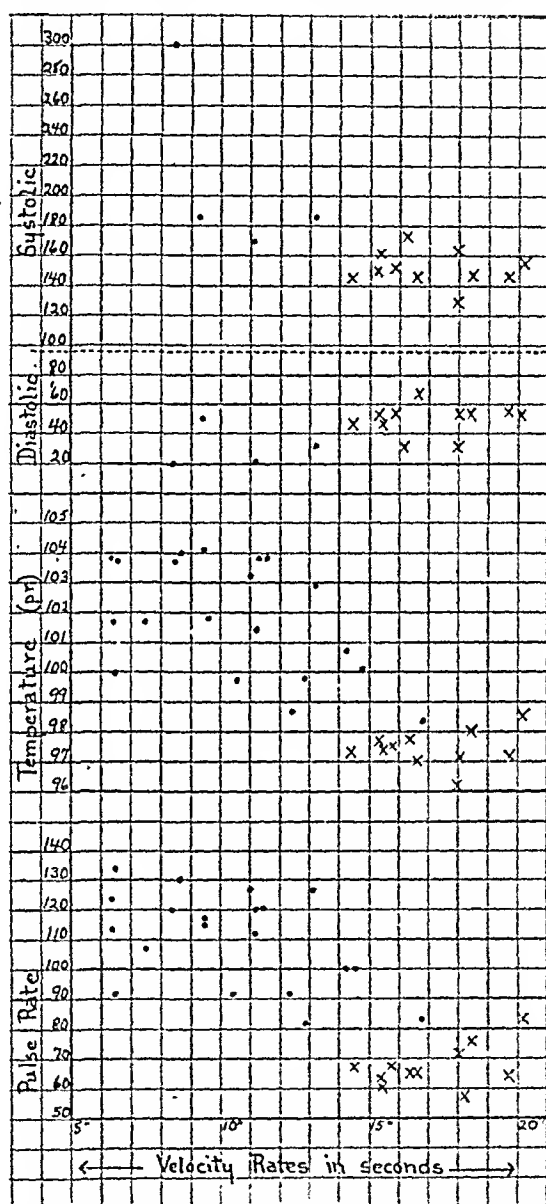


Fig. 6.—Velocity rates in fever produced by diathermy (Patient M. M.). "X" equals basal rates included for comparison.

A comparison of the average velocity rates and other clinical findings obtained on both patients during diathermy fever reveals more marked changes in the velocity of flow and pulse rate of the patient with luetie heart disease, M. M., than of the patient with no cardiac pathology. This is seen in Table II.

With the induction of therapeutic fever in each patient there occurred, as a rule, a drop in the diastolic blood pressure frequently

TABLE II

A COMPARISON OF THE INCREASES IN THE PULSE RATE, BODY TEMPERATURE, AND VELOCITY OF BLOOD FLOW DURING DIATHERMY FEVER

(BASED ON AVERAGE VALUES)

	BEFORE FEVER			DURING FEVER			INCREASE		
	PULSE	BODY TEMP.	VELOCITY	PULSE	BODY TEMP.	VELOCITY	PULSE	TEMP.	VELOCITY
S. C.	71	98.3° F.	14.8"	111	104.8°	10.2"	56%	6.5°	45%
M. M.*	65	97.5° F.	16.7"	124	103.8°	8.8"	91%	6.3°	90%

*Patient with luetic heart disease.

approaching zero, and a slight rise in the systolic blood pressure with a resulting increase in the pulse pressure. Not many blood pressure readings were obtained during fever treatment of the patient with luetic heart disease, but on one occasion the pulse pressure increased from a basal level of 100 mm. mercury to a level of 280 mm. mercury at 103° F.

DISCUSSION

The individual variations in the basal velocity of the blood flow as shown by the repeated results on the two patients undergoing therapeutic fever are greater than those obtained by other workers on normal patients. Blumgart and Weiss⁸ determined the basal velocity of blood flow on fifty-three normal patients by the radioactive method and found variations of from four to five seconds only on two patients on repeated tests. Tarr and his coworkers⁹ utilizing the decholin procedure found individual variations of only three seconds on a group of sixty normal men and women. Robb and Weiss¹⁰ made from three to eight determinations of the circulation time by means of the sodium cyanide method on the same day on a group of eight patients and found variations, as a rule, of two seconds or less. On three subjects variations of three and four seconds were obtained and were attributed to restlessness during the test. Though it has been shown by the above named workers that interindividual variations in the basal velocity of blood flow are fairly large, as much as twelve seconds, no conclusions can be drawn as to variations in any one individual over a lengthy time interval, i.e., days or weeks. Search of the literature has not revealed any work done along these lines.

The following factors can be considered as possibly responsible for the greater-than-normal variations of the basal blood flow in M. M. and S. C. during their course of therapeutic fever.

a. Changes in the basal metabolic rate due to repeated therapeutic fever altering the basal velocity of blood flow.

b. Emotional factors accompanying the test altering the metabolic rate.

c. Myocardial changes as a result of therapeutic fever.

The constancy of the basal metabolic rate, allowing for plus or minus 10 per cent individual variations, is a well-established fact.¹¹ Basal metabolic rates were determined frequently (80 determinations) upon a patient in this clinic who had been given fifty diathermy treatments consisting of about 250 hours of diathermy fever over a period of seven months, and it was apparent that repeated diathermy fever therapy had no residual effect upon the basal metabolic rate (unpublished data).

The increase in pulse rate and velocity flow of the normal patient during the latter half of his treatments may indicate an increase in metabolic rate due not to therapeutic fever but to uncontrolled factors, such as increased muscle tension and emotion, in spite of evident basal conditions. These factors, especially the latter, tend to raise the pulse level and the basal metabolic rate.¹² Landis,¹³ however, concluded that emotional conditions do not necessarily affect the metabolic rate. The changes in metabolic rate which did occur during "emotion" and "upset" experiments Landis attributed partly to muscular activity, but for the most part to vascular changes involving the volume flow of blood. Segal and his coworkers¹⁴ found little or no change in the basal metabolic rate as a result of emotion in a group of normal patients. It appears rather illogical to assume that S. C. became more tense or "upset" emotionally as treatments were repeated since experience shows that patients tend to become accustomed to the procedure. In addition, it appears that the variable velocity rates obtained on this patient require an explanation depending on factors other than the basal metabolic rate since a basal pulse rate from 71 to 73 per minute, suggesting a fairly fixed metabolic rate, showed variations in six velocity rates of from 11.1 to 16.2 seconds.

It is improbable that therapeutic fever as used in this clinic should cause myocardial damage, and experience in a large group of cases indicates that damage does not occur. Damage to heart muscle should manifest itself by an increase in basal pulse rate (damage to the neuromuscular bundle would slow the heart) and by a slowing of the basal velocity of blood flow. In neither patient were these two findings present together as treatment continued. The upper limits of temperature in therapeutic fever as carried out on these two patients are at a level at which no destruction of muscle tissue occurs. Therapeutic fever in itself possesses no toxic effect. Repeated fever therapy given to M. M., the cardiac patient, caused a slowing of pulse rate and an increase in velocity flow as treatment continued, changes which resemble closely the stimulating effect of digitalis therapy upon a failing myocardium.¹⁵ The first few basal velocity rates on this pa-

tient were slower than the normal rates obtained by Gargill² and Tarr and his coworkers⁹ in their series by the decholin procedure, and Blumgart and Weiss¹⁶ have shown that in luetic heart disease with aortic regurgitation a slow velocity rate may be the precursor of a failing heart even before any subjective symptoms occur.

The changes in basal pulse rates and velocity of flow in both patients are, therefore, not due to residual effects of therapeutic fever upon the basal metabolic rate or to myocardial damage but are probably the results of a specific effect of therapeutic fever upon the cardiovascular system, resulting among other things in better heart muscle tone.

The variations in the velocity of the blood flow of each patient at different temperature levels during therapeutic fever may be due to (a) fluctuations in the metabolic rate occurring at these temperature levels,¹⁷ or (b) variable changes in the cardiovascular system (changes in blood volume and viscosity, differences in blood pressure levels, etc.), especially brought on by changes in the wet bulb temperatures of the enveloping air blanket.¹⁸ The less marked increases in the velocity of flow which occur as the body temperature is falling resemble in a way the metabolic rate, the metabolic rate for similar temperature levels during therapeutic fever being less when the body temperature is falling than when rising.¹⁷ The increases in the velocity of the blood flow obtained in the above reported experiments are less marked than those obtained by Kissin and Bierman⁴ by the sodium cyanide method on a group of patients undergoing radiotherm hyperpyrexia. The reason for this is not apparent.

The smaller increases in the velocity of flow occurring during fever induced by typhoid vaccine in S. C. may be due to the absence of the hot, moist, insulating air blanket present in diathermy and electric blanket fever and its effect upon the peripheral blood flow. Hewlett¹⁹ has shown that, when perspiration occurs on exposure to increased environmental temperatures, the peripheral circulation, approximating about 30 per cent of the total circulation at this time, is increased as much as 400 per cent and influences the general circulation considerably. These conditions exist during diathermy and electric blanket fever in which the surrounding air temperature is high (120° to 135° F.) and diaphoresis is quite rapid and marked. During typhoid vaccine fever, however, the peripheral circulation is slowed as body temperature is rising and increased above normal as it falls.¹⁹ The marked differences occurring in the peripheral blood flow during diathermy and electric blanket fever, on the one hand, and typhoid vaccine, on the other, may explain the less marked increases in the velocity of blood flow occurring during the latter type

of induced fever. The smaller increases in the velocity of flow during typhoid vaccine fever cannot be explained by differences in the metabolic rate since it has been found that the rises in metabolic rate for these three types of induced fever (excluding the typhoid vaccine chill) are nearly the same.¹⁷

Barr and his coworkers²⁰ have shown that during the typhoid chill a marked increase in basal metabolic rate ranging up to 200 per cent occurs. Metabolic rates determined upon a patient in this clinic during the typhoid chill ranged from 125 to 180 per cent above normal. The pulse rates obtained on S. C. during the chill are in no way indicative of this great rise in metabolism. The percentage increases in the velocity of blood flow also do not parallel the increase in metabolic rate, the latter finding being contrary to the findings on patients with thyrotoxicosis by Blumgart and his coworkers,³ who found the increase of the velocity of pulmonary blood flow proportional to the height of metabolic rate. Their results showed that an average increase of 33 per cent in metabolic rate was accompanied by an average increase of 61 per cent in the arm-to-arm blood flow. The arm-to-arm circuit (arm-to-heart circuit plus the pulmonary circuit) utilized by Blumgart and his associates is about equal in distance to the arm-to-tongue pathway utilized in the decholin procedure, and a fairly good comparison can be made. The percentage increase in the velocity of flow over the arm-to-tongue pathway during the typhoid chill at a period when the increase in metabolic rate is from 100 to 200 per cent above basal conditions is less than the percentage increase found by Blumgart and his coworkers in the arm-to-arm velocity time at a much lower metabolic level in thyrotoxicosis. This difference may be due to the increased peripheral blood flow occurring in thyrotoxicosis²¹ as opposed to the diminished peripheral flow occurring during the chill of typhoid vaccine.¹⁹

The more rapid pulse and velocity rates obtained on the patient with luetic heart disease during diathermy fever when compared with those of the patient without cardiac disease may be explained by the observation that patients with organic heart disease require more oxygen to perform a given amount of work than do patients with normal hearts.²² Metabolic rates obtained on a group of patients in this clinic during diathermy fever revealed a greater increase in metabolism for a given rise in body temperature when heart disease was present than when absent (unpublished data). That the velocity of blood flow during fever is a better index of cardiac stress than the pulse rate is shown by the following:

a. In a well-compensated patient with aortic insufficiency, cardiac hypertrophy, and general paresis, a temperature of 104° to 104.8° F.

(R) was accompanied by an increase in pulse rate from 69 to only 94 per minute, even with marked discomfort of the patient. The velocity of blood flow showed increases as high as 95 per cent above basal level.

b. A second patient with general paresis and no apparent heart disease who tolerated a temperature of 104.8° to 105.8° F. (R) with a minimum of discomfort, showed an increase in pulse rate from a basal level of 75 to 124 per minute, with the velocity of blood flow showing an increase of only 40 to 54 per cent. Though the pulse rate of the patient with luetic heart disease showed an increase of only 36 per cent, the velocity of flow increased as much as 95 per cent, whereas an increase in pulse rate of 65 per cent in the patient without heart disease was accompanied by an increase of only 40 to 54 per cent in the velocity of blood flow.

It has already been shown that there is a disproportionate increase in pulse rate and velocity of flow for nearly similar rises in body temperature between the patient evidently free from heart pathology and the one with luetic aortic insufficiency and cardiac hypertrophy. The response of the heart in therapeutic fever as shown by changes in the blood pressure, pulse rate, and velocity of flow will no doubt depend largely upon the functional capacity of the heart. It appears, then, that the responses of the cardiovascular system to therapeutic fever, induced either by diathermy or the electric blanket, can be used as an index of the capacity of the heart to respond to conditions of stress. The functional efficiency and reserve of the heart can be estimated by inducing a rise in body temperature to some arbitrary level (100° to 102° F.) under basal conditions and noting the changes in the cardiovascular system which occur. A comparison of the changes in the basal metabolic rate and the cardiovascular system (systolic, diastolic and pulse pressures and especially the velocity of the blood flow) with those obtained before fever therapy should enable one to estimate the heart capacity and reserve. Repeated tests during the evolution of any underlying heart pathology would allow an estimate of the direction in which the efficiency of the heart was proceeding.

SUMMARY AND CONCLUSIONS

Therapeutic fever was induced by means of diathermy, electric blanket, and typhoid vaccine in two patients with general paresis, one apparently free from heart disease, the second with luetic aortic regurgitation and cardiac hypertrophy, and the arm-to-tongue velocity time determined by the decholin method.

During the second half of the fever treatments of the patient with an apparently normal heart an increase in the basal velocity of flow

occurred and was accompanied by an increase in the pulse rate. The basal velocity of blood flow of the patient with luetic heart disease tended also to increase as fever therapy continued but was accompanied by a slowing in the pulse rate.

The conclusion is suggested that the changes in the basal velocity of blood flow and pulse rates of both patients are due to the beneficial effects of therapeutic fever upon the myocardium, the changes in the patient with luetic heart disease resembling those characteristic of digitalis therapy.

Therapeutic fever caused an increase in the velocity of the blood flow in both patients, but no absolute quantitative relationship was found between the percentage increases in the velocity of flow and the degree of temperature rise. The increases in the velocity of flow were least marked during typhoid vaccine fever.

Based on average values for nearly similar rises in body temperature in diathermy fever, the increase in the velocity of the blood flow of the patient with luetic heart disease was much greater than that of the patient with an apparently normal heart.

The response of the cardiovascular system to induced fever is proposed as a new test of cardiac function and reserve.

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Department of Clinical Reports

AN UNUSUAL T-WAVE IN AN ELECTROCARDIOGRAM

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IN THESE days, when much time is being devoted to the investigation and experimental study of the T-wave, it is important to have all recorded varieties on the record. With this in view the present communication is made. It was recorded nearly ten years ago; the whole episode occupied less than sixty seconds and, since it was observed, no other similar record has been seen, nor has there been found any mention of such an one in the literature of either clinical or experimental medicine.

The patient presented himself in May, 1926, complaining of brief attacks of tachycardia which had occurred at infrequent intervals. An attack on the preceding day had continued for an hour, and had made him so uncomfortable that it frightened him to such a degree that he was persuaded to seek advice.

He said he was forty-two years of age. He had had measles and chickenpox as a boy. He denied having had syphilis and said the Wassermann test had been negative. He had had gonorrhea and had received appropriate and effective treatment. He had had extractions of many of his teeth for pyorrhea and alveolar abscesses. He had had a chronically infected antrum which had been drained but not before he had developed a generalized arthritis, with some limiting of motion of most of his joints, including the maxilla. Because of frequent attacks of suppurative tonsillitis he had had a tonsillectomy at the age of thirty-six years. He admitted a liberal use of alcohol, tobacco, and coffee.

The examination showed a well-nourished man of good color, six feet four inches high, who weighed 210 pounds. He had considerable difficulty in moving because of the limited motion of his joints. He could separate his teeth about one centimeter. The breathing was normal, and there were no abnormal findings in the lungs. The peripheral arteries were not thickened, and the apex of the heart was felt in the fifth interspace, 10 cm. to the left of the midsternal line. The rhythm was regular at 68 per minute. The heart sounds were not abnormal, and there were no murmurs. The fluoroscopic cardiac shadow measured 13.6 cm., with the interthoracic wall measurement 28.3 cm. The aortic arch seemed somewhat denser than usual. The abdomen was not abnormal. The deep reflexes were present and active. The physical examination otherwise was negative.

The electrocardiogram (Fig. 1) taken on May 17 showed a regular sinus rhythm at a rate of sixty, a P-R conduction time of 0.16 sec., and a QRS duration of 0.08 sec. In Lead I, the P-wave was positive, 1 mm. in all cycles. The R-wave varied in voltage with respiration from 5 mm. to 9 mm., and the S-wave varied from 1 mm. to 2 mm. The T-wave was positive 1 mm. and recurred in the same form until the third cycle

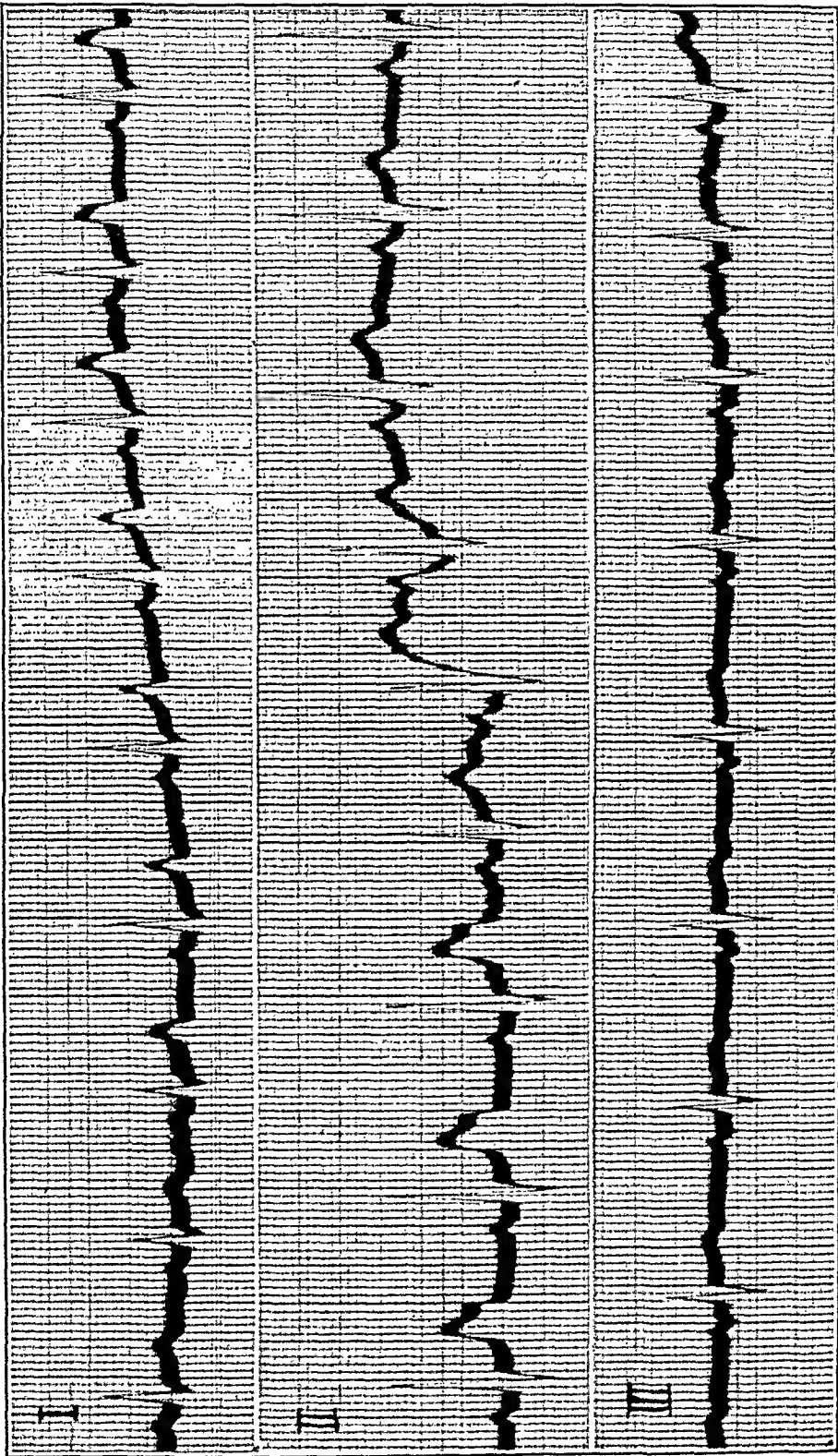


Fig. 1.—A. P. O. May 17, 1926.

in the figure, when there was an abrupt change consisting in an elevation to 3.5 mm. in height, and a sharpening in contour, gradually widening at the base and becoming blunter until, at a height of 5 mm., it had a peak at two levels and a base 0.12 sec. in duration. This truncated conelike form continued to the end of the record. Lead II shows a sequential sinus rhythm, with a P-wave of 1 mm. in height and 0.08 sec. in duration; an R-wave of 14 mm. to 15 mm., changing voltage with respiration; an S-wave of 5 mm. to 6 mm., the first limb being the downward continuation of the second limb of R. Following S is an isoelectric portion of about 0.12 sec. duration which at the end curves upward into a T-wave of two levels and a base of 0.22 sec. duration. This form of

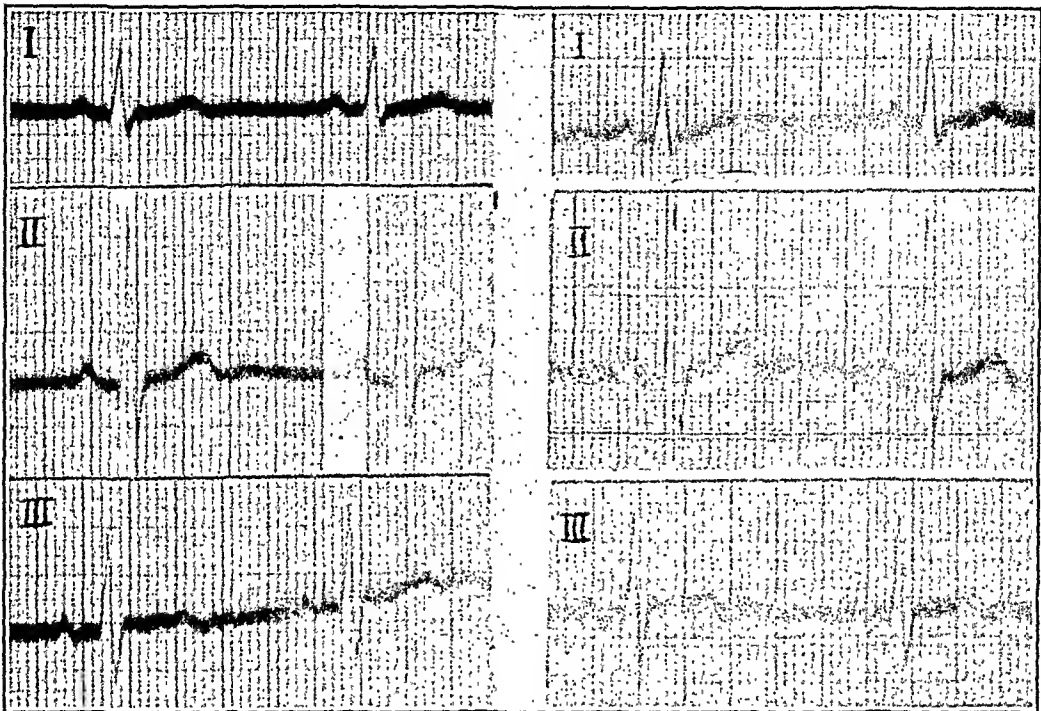


Fig. 2.

Fig. 3.

Fig. 2.—A. P. O. May 21, 1926.

Fig. 3.—A. P. O. May 28, 1926.

T continues until there is an abrupt cessation and a return to a T-wave with a slow diphasic form, the first portion being positive for 3 mm. to 2.5 mm., and the second negative for 1 mm. The P-wave after the cessation of the abnormal T-wave has a different conformation. The elevation of the base line at this point may have been due to motion of patient's arm. Lead III reveals a sequential sinus rhythm, with a P-Q conduction time of 0.18 sec. P in the first cycle is diphasic but becomes completely positive with inspiration. R_s varies from 7 mm. to 9 mm. The S-wave varies slightly with the changes in R. T is positive and diphasic, with a gentle curve.

While the first and second leads were being recorded, the patient said he had a "quivering feeling" in his left chest and put his hand up to the

precordium at about the moment of cessation. There was no objective change visible at the chest area or in vasomotor skin color changes.

Two subsequent records (Figs. 2 and 3) show no abnormal complexes though there is some increase in the voltage of the R-waves.

The patient has continued to carry on without further attacks or the development of any cardiac incapacity.

COMMENT

The unusual T-waves cannot be artefacts since they originate in Lead I and continue in relation to the T portion of the cycle through the Lead I time interval and during the short interval of changing leads into Lead II and up to its cessation in Lead II, with abrupt discontinuance. The phenomena were accompanied by subjective sensations.

The most plausible explanation from experience is the suggestion of a paroxysmal auricular tachycardia with two-to-one auriculoventricular block. There are several unusual features. The alternation in the time intervals from P to T and from T to P. The time P to T is regular and equal to 0.48 sec., but the T to P time varies from 0.4 sec. to 0.28 sec., as the diastolic time varies. The apex of T is a fixed time after P but there is a variable time interval between apex of T and the succeeding P. This indicates an unusual auricular-impulse-formation behavior if it originates in the sinus but is probably not unusual if it is inherent in the factors which cause T. When a P-wave falls on a T-wave, the summation of the two approximates that of the usual P degree but does not otherwise change the form of T. In the recorded T, the sum is much greater in voltage and much longer in duration and thus has the form of a truncated cone rather than a pyramid with smaller pyramid superimposed.

The conformation, time incidence, and duration suggest that the phenomena may be due solely to changes in that portion of the conduction system producing the T-wave and not to an algebraic summation of P plus T.

SUMMARY

The record presents a T complex differing in form from the expected complex of the algebraic sum of P plus T.

The conformation of the T resembles a summation occurring in a paroxysmal auricular tachycardia, with a two-to-one block. If this is true, the rhythm of the P-wave is not regular, though the time between the P and T is regular, for the time from T to P is variable.

The variations in the form of T and its increased duration suggest the conception of a disturbance in the function of that portion of the conduction system producing the T-wave.

After this report was prepared for publication, the opportunity presented and Dr. Harold E. B. Pardee examined the record and has kindly furnished the following note:

"The record shown me has one additional noteworthy feature which seems important. The QRS-T duration in Lead I varies between 0.40 and 0.42 sec. and does not change materially in most of the cycles showing the peculiar deformity of T. In the eighth cycle, however, it reaches 0.44 sec. In Lead II the QRS-T duration is 0.50 sec. in the cycles with deformed T and varies between 0.40 and 0.42 sec. in the others. In these prolonged cycles one can observe an appearance like the end of the T-wave at 0.42 sec. after the beginning of QRS. This suggests the presence of an artefact. If one could suppose that an extracardiac potential were developed at a point in the first beat of Lead II at 0.22 sec. after the peak of R and ended 0.44 sec. after this peak, having caused an elevation of about 4 mm. in the zero of the record for this length of time, one could explain this deformity. But such an extracardiac potential could not be developed so regularly with each beat in such an exact relation to the preceding QRS group. In Lead I its onset varies between 0.28 and 0.32 sec. after the beginning of QRS and in Lead II between 0.26 and 0.30 sec. after this event. It seems that for this reason we must attribute this peculiarity of T to some variation in the deactivation processes in the ventricular muscle."

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ELECTROCARDIOGRAPHIC CHANGES IN TRICHINOSIS*

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CASES of trichinosis with clinical and electrocardiographic evidence of myocardial damage are rare. Within the past year there have been two references in the literature to electrocardiographic changes in trichinosis.

There are in the literature a few references to involvement of the myocardium on histological examination in such cases. In one case a questionable trichina has been noted in the myocardium.¹

Zoller² in an excellent article reports that it is impossible to find trichinae after the second week in the myocardium of guinea pigs. Dunlap and Weller³ fed white rats trichinae larvae and noted that there was an absence of encysted larvae in the heart muscle. They believe that the active migration of the larvae to the myocardium, and not a toxic substance, produced the myocarditis. They are unable to explain the lack of encystment.

With these changes in the tissues it is surprising there are so few references in the literature to clinical changes. Spink⁴ has recently given an excellent review of this subject. Master and Jaffe⁵ have noted some electrocardiographic changes. Cheney⁶ reports a case without signs of circulatory failure but with extreme hypotension. The electrocardiogram showed occasional extrasystoles.

A case of trichinosis has recently been observed in Lakeside Hospital with striking changes in the contour of the T-waves of the electrocardiogram. Pardee⁷ mentions that T-wave changes may occur in trichinosis.

A well-developed, twenty-seven-year-old white man entered the accident ward at Lakeside Hospital in a stuporous condition. Twelve days before admission to the hospital, the patient was sick and vomited. He worked for three days and then had generalized aching and more frequent vomiting. The eyelids were swollen but the swelling subsided in two or three days. The day before admission he was somewhat stuporous and drowsy. His family physician stated that there had been some muscular twitching and some pain in the abdomen. Later history revealed the fact that the patient frequently ate cold pork pie and pigs' feet.

Physical examination revealed a stuporous man with loss of deviation of the eyes to the left. There was poor convergence. There was left hemiparesis, with hyperactive reflexes, a positive Babinski response, and ankle clonus. Left facial paralysis was present. The blood pressure was 88/68. The leucocyte count on admission was 26,500 with 62 per cent of eosinophiles. The blood and spinal fluid Wassermann reactions were negative. Spinal fluid revealed normal dynamics, negative Pandy reaction, and 3 lymphocytes per cubic millimeter. No trichinae were

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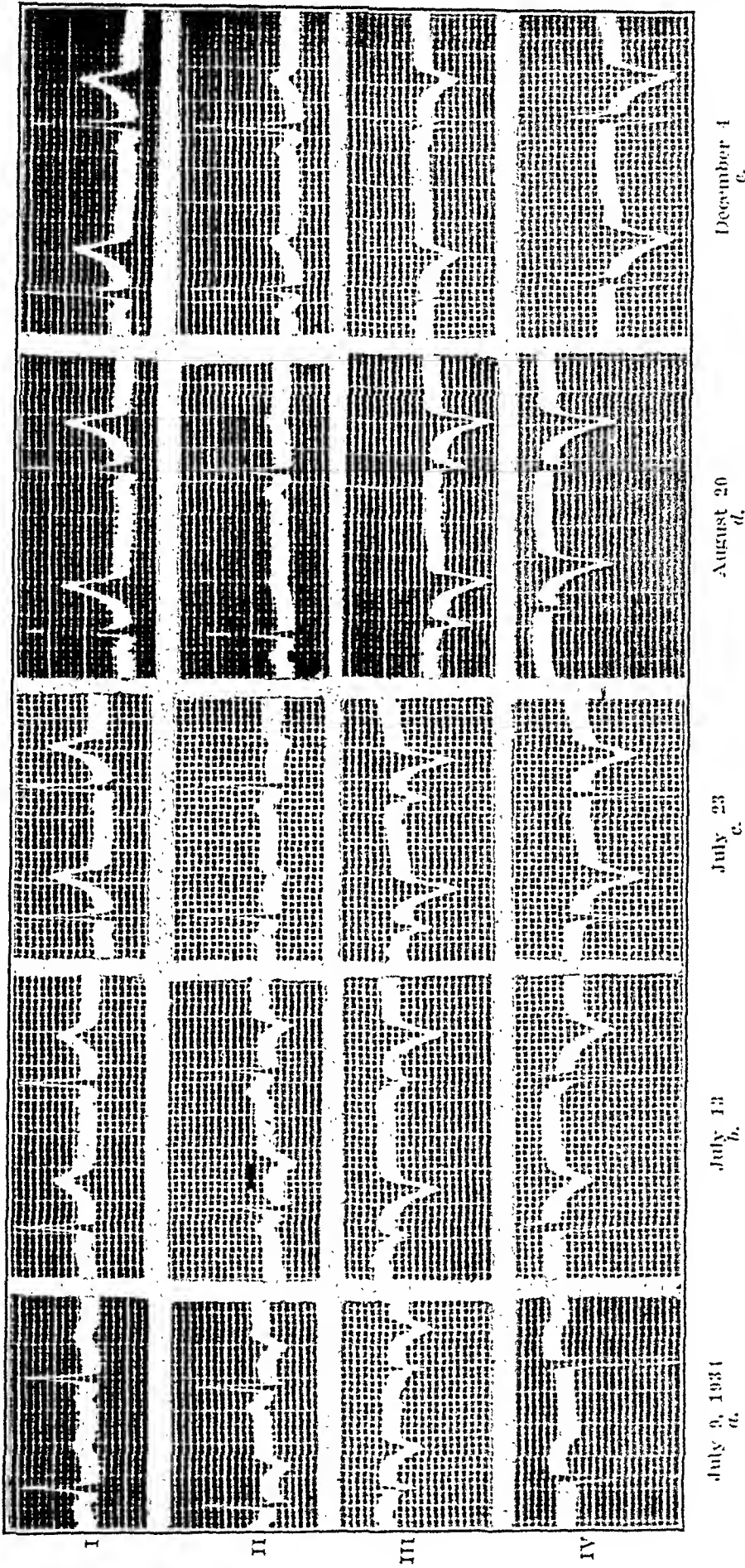


Fig. 1.

found in the spinal fluid. A biopsy of the deltoid muscle revealed an acute myositis and occasional encysted parasites. The patient's temperature was 39° C. on admission and fell to normal by the sixth day.

Throughout the first week of the hospital stay, the patient was stuporous and incontinent. He gradually improved and the abnormal neurological findings disappeared. He was discharged sixteen days after admission to the hospital with no abnormal neurological findings, and a blood pressure of 105/65.

A diagnosis was made of trichinosis of the somatic muscles, of the brain and the meninges and of the myocardium. The electrocardiograms showed variations in the T-waves. The first record, Fig. 1 (a) taken July 9, 1934, showed an inverted T-wave in the second and third leads of the "cove-plane" type. The fourth lead showed slight elevation of the S-T interval with an upright T-wave. Four days later (b) in the first lead the T-wave was higher; the T-wave in the third lead was more deeply inverted; and the fourth lead also showed an inverted T-wave. Ten days later (c) the first lead showed a higher T-wave, the second lead a shallow, inverted T-wave, the third lead no change, and the fourth lead a deeper T-wave. Six weeks subsequent to the first electrocardiogram (d) the second lead showed a slight elevation of the T-wave with no changes in the other leads. Five months after the first record (e) the T-wave in the second lead was slightly more elevated and in the third lead less deeply inverted. The last record, taken July 25, 1935, showed no change from that of December 4, 1934.

SUMMARY

A case of trichinosis with clinical and electrocardiographic evidence of myocardial involvement is reported. The T-waves in the electrocardiogram were inverted in the second lead and upright in the fourth lead. These changes gradually disappeared.

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Department of Reviews and Abstracts

Selected Abstracts

Necheles, H., Frank, R., Kaye, W., and Rosenman, E.: Effect of Acetylcholine on the Blood Flow Through the Stomach and Legs of the Rat. *Am. J. Physiol.* 114: 695, 1936.

The stomach and hind legs of rats were perfused with Locke solution, to which various amounts of acetylcholine were added. In forty-five tests on the stomach, vasoconstriction was obtained forty-four times. The hind legs of rats showed vasodilation in five tests when perfused with acetylcholine. Atropine counteracted the vasoconstrictor effect of acetylcholine on the stomach in every case and the vasodilator effect on the hind legs in all tests but one.

E. A.

Wood, Paul: The Erythrocyte Sedimentation Rate in Diseases of the Heart, *Quart. J. Med.* 5: 1, 1936.

The erythrocyte sedimentation rate has been investigated in 164 cases of heart disease.

Congestive heart failure retards the sedimentation rate regardless of the cardiac pathology and may therefore mask activity of the disease process.

Increased sedimentation rates are found in cases of active rheumatic carditis, syphilitic aortitis, and myocardial infarction. The readings approach normal as the condition improves.

The sedimentation rate is also increased in cases of infective endocarditis and malignant hypertension, but the test is of little value in these conditions.

Angina pectoris of effort, apart from syphilitic cases, is associated with a normal sedimentation rate, angina of rest usually with a somewhat increased rate.

Normal sedimentation rates are found in cases of inactive rheumatic heart disease and of atherosclerosis.

In subjects with hypertensive heart disease the sedimentation rate may be normal or slightly increased.

Pulmonary infarction increases the sedimentation rate.

In the absence of cyanosis, cases of congenital heart disease are associated with a normal sedimentation rate, but with marked cyanosis the rate is abnormally slow.

Mild cases of thyrotoxicosis in which cardiac symptoms predominate are associated with normal sedimentation rates.

AUTHOR.

Behr, W.: The Onset and Duration of Diphtheritic Heart Involvement. *Ztschr. f. Kreislaufforsch.* 27: 793, 1935.

This is based on a study of 230 cases of malignant diphtheria studied clinically and electrocardiographically. Diphtheritic myocardial involvement usually occurs in the first two weeks of the disease. No evidence of new damage occurs after the twenty-first day. The prognosis is especially unfavorable when the heart damage occurs in the first week. The changes are degenerative in character with round cell infiltration. The mortality was 36.5 per cent in the entire series.

Recovery from damage to the heart is rapid, as a rule, when the child survives the infection. The only persistent damage seems to occur when the common bundle or its branches are involved.

L. N. K.

Winans, H. M., and Dunstan, E. M.: Heart Disease in North Texas. Texas State J. Med. 31: 444, 1935.

The impression that rheumatic heart disease in this section of Texas is relatively low in incidence is confirmed.

The impression that, when found, preceding attacks of acute arthritis are relatively low is also confirmed. The percentage incidence of definite attacks of tonsillitis is probably no greater than might be associated with any other disease. Chorea is evidently a negligible part of the rheumatic picture as seen in this study.

Marks, Joseph H.: Calcification in the Annulus Fibrosus of the Mitral Valve. New England J. Med. 214: 411, 1936.

The above report has been presented in order to record a proved case of calcification in the annulus fibrosus of the mitral valve which was correctly diagnosed by roentgen ray during life. It should be recalled that the annulus fibrosus is a figure-of-eight structure which surrounds both the mitral and tricuspid orifices, but the degenerative process which leads to calcification has been noted only in that portion which surrounds the mitral orifice; this is perhaps related to the greater amount of work done by the left side of the heart.

It should be noted that these areas of calcification can be demonstrated with any fluoroscope using 5 milliamperes of current at about 88 kilovolts provided that the examiner searches carefully the deeper parts of the heart through a small aperture and with his eyes fully accommodated. It is well to begin at the auriculoventricular groove on the left border and then gradually move inward and downward at an angle of about 45 degrees. If a mass of calcium is present, its characteristic dancing movement will be noted when the patient holds his breath. Once the mass is found, more accurate localization is made by gradually rotating the patient. Unless the heart rate is too rapid, the exercise of care and patience will be productive of good film records even though the more expensive high speed equipment is not available.

That intra-cardiac calcification may be diagnosed during life and that this calcification may be correctly localized is of real interest to the cardiologist. Difficulty is frequently encountered in establishing the diagnosis of aortic stenosis clinically, but a roentgen demonstration of calcification in the aortic cusps dismisses all doubt. Likewise a demonstrable mass of calcium in the annulus would aid in establishing the prognosis in cases of complete heart-block. The internist and cardiologist may thus expect more from the roentgenologist in the future than a mere statement as to the cardiac size and contour and the appearance of the lung fields.

Kommerell, Burkhard: X-ray Diagnosis of Calcified Heart Valves. Fortschr. a. d. Geb. d. Röntgenstrahlen 53: 34, 1936.

The author describes the findings in ten cases of the calcified heart valves and the technic which should be used to reveal such calcification. The most important part of the examination is the screen examination since the routine film generally does not reveal these calcifications. It is important to use somewhat harder rays than are usually used for examination of the chest and to examine with a very small diaphragm. The observed field should not surpass the limits of the heart shadow. The author found the new hektophan screen which gives especially light

pictures very useful for this purpose. The requirements for the interpretation of this shadow as belonging to the valve are as follows:

1. It should be impossible to project the shadow of these calcifications outside the heart shadow.

2. The relation between the shadows of these calcifications and the heart border should not change during deep inspiration.

3. The movement of these shadows during the heart cycle should be greater than the movement of the heart border.

4. The extension of the movement of these shadows increases in the first oblique.

In order to fix the findings on the film the author recommends the technic used in duodenal examinations.

F. B.

Scott, R. W.: *Systolic Murmur in Clinical Medicine and in Insurance Examination.* Ohio State M. J. 31: 943, 1935.

Excepting physiological systolic murmurs originating over the pulmonic area and extra cardiac respiratory murmurs, all apical and aortic systolic murmurs in adults merit consideration. The faint ones are usually but not invariably benign; louder ones are frequently associated with some type of cardiovascular disease.

An apical systolic murmur for years may afford the only clinical evidence of a damaged rheumatic mitral valve which may go on to stenosis or become the seat of the usually fatal subacute bacterial endocarditis. Aortic systolic murmurs are more often than not a sign of organic disease. The current clinical teaching that tends to disregard the significance of all systolic cardiac murmurs is just as unsound as the older view which associated every adventitious cardiac sound with organic disease. Somewhere between these two extremes lies the truth, and it is from this midposition that an evaluation of systolic murmurs should be attempted.

Kurtz, Chester M., Bennett, James H., Shapiro, Herman H.: *Electrocardiographic Studies During Surgical Anesthesia.* J. A. M. A. 106: 434, 1936.

Electrocardiographic studies were made on 109 patients during 113 surgical operations under various anesthetic agents as follows: cyclopropane, 41; ether, 20; procaine, 13; ethylene, 11; nitrous oxide, 10; vinyl ether, 7; chloroform, 6; and tribrom-ethanol in amylene hydrate, 5. Electrocardiograms were taken as a routine before operation, at frequent intervals during the surgical procedure, during recovery, and ten hours after the operation.

Disturbances of rhythm constituted the most striking changes noted, sinus arrhythmia, extrasystoles, and downward displacement of the pacemaker predominating. A rapid and totally irregular ventricular action, apparently never recorded except under anesthesia, occurred in four cases. Complete heart-block was found twice and paroxysmal auricular fibrillation once. Arrhythmias appeared more frequently in abnormal than in normal hearts. The lowest incidence of arrhythmias occurred with procaine and the highest with chloroform. Of the entire series, only 21 per cent failed to show some type of disturbance. No constant and specific relationship could be established between the occurrence of arrhythmias and the depth of anesthesia or the steps in the surgical procedure.

Variations in the amplitude of the QRS complexes and T-waves, shifting of the ST segment and changes in the P-R interval occurred in the majority of cases and for the most part were of a transient nature.

In a large percentage of cases the electrocardiogram taken ten hours after operation differed in certain respects from the control tracings, and further work will be required to determine the persistence and significance of these changes.

AUTHOR.

Storti, E.: Concerning the Nullpotential-Electrode in Electrocardiography. *Ztschr. f. Kreislaufforsch.* 27: 830, 1935.

The possibility of using a nullpotential-electrode was investigated on an equilateral triangle model. The values of the potentials at the three corners of the triangle were determined, and by applying Kirschhoff's distribution equation, it was shown that the procedure of connecting the three ends of the triangle together as used in man by Wilson and his associates did not give a zero potential. The author demonstrates that the deviation from zero potential is a periodic function of Einthoven's angle α ; zero potential being attained when the angle is 0 degrees, 60 degrees, and 120 degrees. The author concludes that the assumption that the electrode employed by Wilson, Johnson, MacLeod, and Barker is at zero potential requires proof in view of its inapplicability to the models used in his investigations.

L. N. K.

Luft, H.: Electrocardiographic Studies Concerning Left and Right Axis Deviation. *Ztschr. f. Kreislaufforsch.* 27: 793, 1935.

In twenty-nine out of one hundred instances of hypertension there was left axis deviation in the ordinary three leads. None of the twenty-one instances of emphysema showed right axis deviation. However, by utilizing precordial leads with the distant electrode on the right arm, a distinction could be made between these two types of cases. The procedure is to connect the right arm electrode to the right arm terminal and the precordial electrode to the left arm terminal. The maximum potential over the right and that over the left ventricle are determined and the ratio of the two is calculated. The ratio L/R in normals varies between 1.3 and 1.7. In forty-five out of fifty patients with hypertension this ratio was above 1.7. In all twenty-five patients with emphysema, mitral stenosis, or asthma the ratio was less than 1.3. This procedure, therefore, offers a better criterion of determining ventricular preponderance than that obtainable from the standard leads.

L. N. K.

Rabinowitz, H. M., and Kahn, J.: Relationship of Phospholipin Metabolism to Thromboangiitis Obliterans and Its Treatment. *Am. J. Surg.* 31: 329, 1936.

Based on the premise that the thrombotic tendency in thromboangiitis obliterans is due to changes in blood chemistry and coagulability, studies of the phospholipin metabolism have convinced the authors that the pathological process lies there. Although phospholipins are adequately mobilized in the blood stream, they are not properly stored or utilized in the formation of creatine phosphate used in muscle contraction. The changed lecithin-cephalin ratio predisposes to intravascular clotting. This metabolic defect explains the early claudication seen in this disease.

Since the authors have evidence that insulin-free pancreatic tissue extract contains a hormone which exerts a strong influence on phospholipin metabolism, they advocate in the treatment of thromboangiitis obliterans use of that extract plus limitation of lecithin-rich foods.

L. H. H.

Huber, H.: Acquired Defects of the Intraventricular Septum. *Ztschr. f. Kreislaufforsch.* 27: 825, 1935.

This is a report of two autopsied cases, both the result of a rupture following myomalacia due to coronary occlusion. Three other cases from the literature are cited. The acquired defects following myomalacia are located in the anterior apical or midportions of the septum. This is in contrast with congenital defects and acquired ones following endocarditis which are located toward the A-V junction.

L. N. K.

Ernstene, A. Carlton: The Differential Diagnosis of Coronary Artery Disease. J. Kansas M. Soc. 36: 441, 1935.

In the past, in discussions of the differential diagnosis of angina pectoris and coronary thrombosis, emphasis has been placed almost entirely upon the fact that these conditions might give rise to symptoms suggestive of some other pathological state, particularly upper abdominal disease. Only of late have a few reports appeared directing attention to the possibility of erroneously interpreting the symptoms of upper abdominal disease and certain intrathoracic conditions as due to coronary artery disease.

In the present communication are summarized four cases in which the symptoms closely resembled those of coronary thrombosis or angina pectoris. In the first case the symptoms were due to cholelithiasis. In the second, a large esophageal hiatus hernia caused pain suggestive of angina pectoris. In the third, a clinical picture simulating coronary occlusions resulted from pulmonary embolism with acute cor pulmonale, and in the fourth, a dissecting aneurysm of the aorta was mistakenly diagnosed coronary thrombosis. The cases illustrate the diagnostic significance of negative electrocardiographic findings and also indicate the importance of detailed analysis of the patient's symptoms and physical signs. In the future diaphragmatic hernia, upper abdominal disease, dissecting aneurysm of the aorta, and pulmonary embolism with acute cor pulmonale should be excluded before a diagnosis of angina pectoris or coronary thrombosis is made in patients presenting features not typical of coronary artery disease.

Hochrein, Max: Guiding Principles in the Treatment of Myocardial Infarct. München. med. Wehnschr. 82: 1515, 1935.

The diagnosis of myocardial infarct is relatively easy. The prognosis is very grave, the mortality being from 60 to 70 per cent in a large clinical series. Myocardial infarct is usually caused by coronary thrombosis. The author believes that coronary spasm resulting from vagotonia, especially if susceptibility to spasm is increased by nicotine, coffee, digestive disturbances, or meteorism, may be the cause occasionally. The immediate effects of infarction are increased irritability of the myocardium, early rise in blood pressure which is generally followed by a marked fall, evidences of circulatory shock, and certain chemical disturbances, such as occasional hyperglycemia and nitrogen retention in the blood.

The author advocates, in the early stages, sodium luminal 0.2 gm. intramuscularly two or three times a day followed by some other sedative orally on succeeding days. He prefers sodium luminal to morphine as he claims the former improves cardiac circulation. Bed rest is recommended for at least six weeks. Small meals at two-hour intervals are suggested. Intramuscular injection of sympatol 1.0 c.c. is advocated as a circulatory tonic in the early stage, and 20 drops by mouth three times a day is suggested for later use. An attempt to avoid fibrillation by the use of quinidine 0.1 gm. twice a day is suggested. Cardiac failure should be treated by digitalis or intravenous injection of strophanthus and of glucose.

W. B.

Rinehart, James F.: Studies Relating Vitamin C Deficiency to Rheumatic Fever and Rheumatoid Arthritis; Experimental, Clinical, and General Considerations. Ann. Int. Med. 9: 671, 1935.

The experimental basis for the concept that rheumatic fever may be the result of the combined action of vitamin C deficiency and infection is reviewed. Further experimental studies are reported which confirm the original observations that this deficiency with superimposed infection produces in the guinea pig a disease state with many pathological similarities to rheumatic fever. Comparable lesions develop

in the heart valves, the heart muscle, and the joints. The occasional occurrence of subcutaneous nodules remarkably like those of rheumatic fever would appear to complete the pathological similarity.

Evidence is presented that the factor of infection is not specific. Essentially similar lesions develop when different organisms are used as the infecting agents. The same infections do not cause rheumatic type lesions in animals receiving adequate amounts of vitamin C.

It is suggested that vitamin C deficiency may afford the basis for the hemorrhagic manifestations frequently observed in rheumatic fever.

The epidemiological peculiarities of rheumatic fever, notably its social, geographic, and seasonal incidence, might be explained on the operation of a scorbutic factor in the disease.

Evidence indicating not only the existence, but the probable frequent occurrence of latent scurvy is reviewed. The relatively high vitamin C requirements of children, the limited capacity to store the vitamin, and the possible influence of infection or fatigue in depleting this organic reserve are discussed.

Clinical studies in progress are cited that have afforded encouraging data.

On the basis of further experimental studies and clinical and epidemiological data, the thesis is reaffirmed that rheumatic fever may result from the combined influence of vitamin C deficiency and infection.

Gerlach, W.: Rheumatic Mesoarthritis. *Ztschr. f. Kreislaufforsch.* 28: 2, 1936.

The author discusses the differentiation between syphilitic and rheumatic mesoarthritis and reports an autopsied case which is interpreted as being rheumatic mesoarthritis with dilatation of the ascending aorta and aortic arch.

L. N. K.

Beck, E. C., Fowler, J. G., Koenig, E. C., and Bowen, B. D.: Vascular Disease in the Obese Diabetic, and in Non-Diabetics; A Discussion of Arteriosclerosis as a Cause of Diabetes. *Ann. Int. Med.* 9: 662, 1935.

Calcification of the arteries of the lower extremities (demonstrated roentgenologically), which is common, particularly in patients with older, uncontrolled cases of diabetes, is essentially absent in patients with early cases of diabetes and in obese people, some of whom are potential diabetics.

No evidence was found to show that hypertension or retinal arteriosclerosis could be correlated with the obese patient's ability to use glucose. The incidence of hypertension appears to be higher in the older diabetic. We believe, however, that this is essentially related to obesity and not to diabetes.

The proposal that diabetes in older people is commonly caused by sclerosis of the pancreatic blood vessels is discussed. Direct proof that sclerosis of the pancreatic vessels causes diabetes cannot be determined by clinical methods, nor can it be held responsible as a primary cause of diabetes when found at necropsy. Nevertheless, it seems improbable that such sclerosis can be regarded as a general cause for diabetes in older people.

Elliot, A. H., and Nuzum, F. R.: Cholesterol Content of Whole Blood in Patients With Arterial Hypertension. *Arch. Int. Med.* 57: 63, 1936.

The significant finding in this carefully controlled piece of clinical investigation is that uncomplicated arterial hypertension is not accompanied by significant changes in the cholesterol content of the blood.

The cholesterol figures of 53 hospitalized hypertensive patients followed very closely those of a control group of 45 hospital and dispensary patients.

Vascular degeneration and renal impairment associated with the hypertension do not raise the cholesterol level of the blood.

L. H. H.

Gregg, Donald E.: The Phasic and Minute Coronary Flow During Acute Experimental Hypertension. *Am. J. Physiol.* 114: 609, 1936.

Acute experimental hypertension produced by increasing the peripheral resistance, either mechanically or chemically, augments the coronary blood flow. It is the author's tentative concept that as the aorta is compressed and the blood pressure and pulse pressure rise, the heart rate slows, the coronary systolic resistance decreases relative to the aortic systolic, thus permitting an actually greater inflow per beat during ventricular contraction, although the systolic flow relative to the diastolic is decreased. However, the minute systolic flow increases only moderately since, as the heart rate slows, the time occupied by systole is materially reduced. During diastole at the high pressure the diastolic interval lengthens, and the diastolic coronary pressure increases only slightly, with the net result that the diastolic flow per cycle and per minute is tremendously augmented. The conclusion is reached that the dominant factor in increasing the myocardial blood supply in acute experimental hypertension is a combination of mechanical changes, of which the most important is the aortic head of pressure throughout the cycle, together with the relative increase in the time per minute occupied by diastole.

E. A.

Gammon, George D.: The Carotid Sinus Reflex in Patients With Hypertension. *J. Clin. Investigation* 15: 153, 1936.

In a study of thirty-one patients with hypertension of either the essential type or that associated with arteriosclerosis, the carotid sinus nerve endings were found, in accordance with other observers, to cause a depressor reflex when stimulated directly. The response to changes in intravascular pressure within the sinus, contrary to the findings of others, was in the direction usually obtained in normal persons. These observations indicate that a failure of the carotid sinus mechanism is not the cause of hypertension in these patients. The significance of these findings is discussed in relation to nervous factors concerned in hypertension.

Clute, H. M.: Acute Arterial Obstruction From Arteritis. *New England J. Med.* 214: 137, 1936.

The condition described in two cases and cured operatively by the author is one of complete occlusion of a large arterial trunk by an inflammatory process within the vessel. Acute arteritis, being localized, is not to be confused with thromboangiitis obliterans or the chronic occlusive diseases.

The increase of blood supply to the part following resection of the affected area of the vessel is thought to be due to paralysis of the vasomotor nerves to accessory arteries, according to the contention of Leriche. Clute believes that the vasospastic sympathetic nerves are stimulated by the diseased artery.

L. H. H.

Jones, Tudor: The Structure and Mode of Innervation of Capillary Blood Vessels. *Am. J. Anat.* 56: 227, 1936.

There is nothing exceptional in the histological constitution of the capillary blood vessels. They consist essentially in a neuromuscular mechanism of the same nature as the walls of the larger vessels and contractile viscera generally. Rouget's cells belong to the nervous, not to the contractile, element in this complex. The contractile elements are ordinarily smooth muscle cells. The first sign of physiological activity in young vessels is the extension of elements in continuity with the nervous system in their neighborhood.

E. A.

Russow, E.: The Blood Supply of Hypertrophic and Atrophic Hearts. *Zeitschr. f. Kreislaufforsch.* 28: 41, 1936.

The total cross-section area of the three main branches of the coronary is increased in hypertrophied hearts and decreased in atrophied ones, and there is a parallelism between heart weight and the total cross-section area so measured. The media of the coronary arteries, but not the intima, is increased in thickness when the arterial pressure is elevated. Apparently, when advanced coronary arteriosclerosis is absent, the blood supply of hypertrophied heart is better than that of the normal as far as the caliber of the large coronary arteries is concerned. This report is based on a study of 45 hearts.

L. N. K.

Kommerell, Burkhard: Symptomatology of Aneurysms of the Abdominal Aorta. *Röntgenpraxis* 8: 25, 1936.

This is a report of one case in which the x-ray examination showed a tumor mass which pushed forward the cardiac part of the stomach and produced a narrowing of the cardia. The necropsy revealed a dissecting aneurysm of the abdominal aorta.

F. B.

Putts, B. Swayne, and Bacon, Ralph D.: Large Aneurysm of the Descending Thoracic Aorta With Retrosoas Extension. *Am. J. Roentgenol.* 35: 59, 1936.

A case is reported of aneurysm of the lower thoracic aorta in a woman. The aneurysm had been demonstrated roentgenologically for more than four years and probably had been present for at least eight years. It originated from the posterior wall just above the diaphragm and extended behind the diaphragm at its last vertebral attachment to become largely a retrosoas mass. The aneurysm caused erosion of the lower four dorsal and the first lumbar vertebrae and the eleventh and twelfth ribs.

E. A.

Bell, James: Blood Pressure and Aortic Aneurysms. *Irish J. M. Sc.* Dec., 685, 1935.

The factors responsible for the difference in the systolic blood pressure of the brachial arteries associated with aortic aneurysm are: (1) occlusion of the orifice of the innominate or left subclavian artery, due to the distorting effect of the aneurysm or to blood clot, (2) diminution in amplitude of the pulse wave, produced by passage through the aneurysm, and (3) loss of kinetic energy in the aneurysm.

E. A.

Strombeck, J. P.: The Late Results of Embolectomy Performed on Arteries of the Greater Circulation. *Acta chir. Scandinav.* 77: 229, 1935.

In a series of 327 operations performed in Sweden from 1912 to 1932 for the removal of emboli from the arteries of the greater circulation, 63 per cent of the patients died in hospital, 18 per cent were discharged improved after amputation, and 19 per cent had good circulation on discharge. Three-fourths of the latter successful cases were alive one year after the operation, one-half after three years, one-third after five years, and one-eighth after ten years. The length of the survival period seems to depend particularly upon the character of the cardiac affection and also upon the age of the patients, as well as the more accidental factor of danger for new emboli. There is a striking tendency toward cerebral circulatory disturbances (probably emboli in most cases) and emboli in the viscera and extremities long after the first embolism.

Working capacity was best in those who had sufficient vitality to survive the procedure for a fairly long period. Among the half of the series who lived more than three years after a successful operation, about 30 per cent enjoyed rather good working capacity while 20 per cent could not work at all. About 10 per cent of the other half of the patients with successful cases who died in less than three years after operation were able to work rather well for some time, but at least 70 per cent were quite incapable of working.

The local result in the portion of the body operated upon was in most cases very good. Small areas of necrosis, sensory disturbances, or peroneal pareses occurred in one-eighth of the cases, and mild subjective symptoms, such as numbness and paresthesia, in about one-half.

Gurin, David, Bulmer, J. W., Derby, Richard: Dissecting Aneurysm of the Aorta. New York State J. Med. 35: 1200, 1935.

A case is reported in which surgery relieved arterial obstruction of an extremity due to a dissecting aneurysm of the aorta. A diagnosis of the occlusion of the right external iliac and femoral arteries had been made. It was felt that, in spite of marked hypertension and cardiovascular and renal damage, the operation might prevent an otherwise inevitable gangrene of the extremity.

Two and a half hours after the onset of symptoms the right femoral artery was exposed under local anesthesia. At the beginning of the operation a faint pulsation could be felt in the femoral artery. On exposing the vessel no pulsation was visible or palpable. Its wall was intact, and no mass could be felt in the lumen. Aspiration with a fine needle revealed bright blood under markedly diminished pressure. The wound was closed, and under nitrous-oxide oxygen and ether anesthesia the abdomen was opened. The right external iliac artery when isolated three inches above Poupart's ligament was found to have an infiltration of dark blood in its lateral third, extending as far as could be seen in both directions. An impact was transmitted along the artery from above with each heartbeat, but there was no expansile pulsation in any part of the vessel. Rubber-padded clamps were placed on the artery above and below to prevent any influx of blood. Then a longitudinal one-inch incision was made into the anterior surface, which appeared unaffected by the hemorrhagic extravasation. Upon opening the vessel, an atheromatous mass was encountered completely plugging the lumen, which had been narrowed by the dissecting hemorrhage. The intima and media opposite the atheroma were incised from within the vessel. A small curved Kelly clamp was inserted through this incision into a space between the media and adventitia. From this came a steady flow of dark unclotted blood. With the escape of this blood the obstruction was relieved, and when the proximal clamp was momentarily released, there occurred a spurt of bright arterial blood from the incision. The incision into the vessel was closed with interrupted suture of greased silk. When the clamps were removed an expansile pulsation was visible throughout the external iliac artery.

The diagnosis of dissecting aneurysm should be suspected when an individual, usually male, usually with history or evidence of severe hypertension, suddenly develops pain at the level of the precordium without evidence of acute myocardial damage by the electrocardiogram, fall in blood pressure, or marked rise in pulse. Often the pain in these cases is more severe over the thoracic spine or in the epigastrium than under the sternum. The diagnosis should be made when, following the above, signs of acute arterial blockage or internal hemorrhage develop.

Kinsman, J. Murray, and Moore, John Walker: The Hemodynamics of the Circulation in Hypertension. *Ann. Int. Med.* 9: 649, 1935.

Using the dye-injection method of measuring the cardiac output and related factors, the authors studied 44 cases with normal cardiovascular systems, and 75 cases of hypertension subdivided into: 14 "undecompensated" cases which had never shown any signs or symptoms of congestive failure; 18 slightly, 7 moderately, and 15 severely "decompensated" cases; and 21 "compensated" cases, which had previously been decompensated, but which at the time of the test were perfectly compensated.

A large number of the functions of the circulation were studied simultaneously.

In hypertension in which congestive failure has never appeared the venous pressure is nevertheless likely to be definitely increased over normal, and the vital capacity reduced; the velocity of blood flow, the cardiac output, the stroke volume, and the number of heartbeats required to clear the heart and lungs of blood are *essentially unchanged*, while the work of the heart is *tremendously increased*.

As congestive failure appears and increases, the venous pressure progressively rises and the vital capacity falls; the velocity of blood flow becomes very markedly reduced; the cardiac output and stroke volume are greatly diminished; the number of heartbeats required to clear the heart and lungs of blood is markedly increased; and the heart work becomes reduced even to far below the normal value.

As compensation becomes reestablished, there is a tendency for all these functions to return toward normal, and the venous pressure does return to normal, but the vital capacity remains considerably reduced, as do the velocity of blood flow, the cardiac output, and the stroke volume; the number of heartbeats required to clear the heart and lungs of blood remains considerably increased, but the heart work becomes normal again or nearly so.

The results for volume of actively circulating blood in heart, lungs, and great vessels and total circulating blood volume are not striking but are parallel. In general, before congestive failure develops, there is no essential change in either; as congestion develops, they both progressively increase slightly; as compensation becomes reestablished, they increase greatly and significantly.

These results apply to the group as a whole. Individual cases show marked variations from the trend of the group as far as isolated functions are concerned, as, for example, a large output with a low vital capacity and a high venous pressure. This calls attention to the necessity of studying many of the functions of the circulation simultaneously, instead of only a few.

In the decompensated cases, rest alone causes a definite improvement in most of the functions enumerated, but the improvement from digitalis is very much more marked.

AUTHOR.

Wohl, Michael G., and Ettelson, L. N.: III. Studies in Obesity: Effect of Dinitrophenol on Blood Velocity. *J. Pharmacol. & Exper. Therap.* 55: 439, 1935.

In 33 obese patients, the arm-to-tongue circulation time was measured by the intravenous saccharin method. The average of the group was 13.3 seconds, essentially normal figures.

In fourteen of the group dinitrophenol (1-2-4) was given, and further determinations of the circulation time were made. In seven patients an increase in blood velocity was noted, the average acceleration being 3.3 seconds per patient.

Further studies are indicated to determine the manner in which such speeding up of the blood flow is brought about.

Gauer, O.: Pulse Wave Velocity in the Aorta and the Arteries of the Leg of Man. *Ztschr. f. Kreislaufforsch.* 28: 7, 1936.

Optically recorded pulses from the subclavian artery along the course of the abdominal aorta and the femoral arteries were made. The time of the rise of the pulse wave in these various locations was determined. As a result of 250 measurements on a twenty-four-year-old healthy male subject, the author concludes that the pulse wave velocity is the same in the thoracic aorta when standing and reclining, viz., 3.8 to 4 meters per second. In the leg arteries the pulse wave velocity is 12 to 13 meters per second when the subject is standing and below 8.5 meters per second when the subject is reclining. The observations were confirmed with only minor variations in a second normal subject. The pulse wave velocity in the peripheral vessels is modified greatly and abruptly by light pressure.

L. N. K.

Markovits, F.: Estimation of Blood Volume by Means of Blood Sugar Determinations. *Ztschr. f. Kreislaufforsch.* 28: 17, 1936.

Blood sugar is determined by the Hagedorn-Jensen's method on an empty stomach. Then 10 c.c. of 40 per cent dextrose solution is injected intravenously, and the blood sugar is determined 2 minutes later. The blood volume is calculated by dividing 40,000 by the milligram percentage rise in the blood sugar. This method was found to check fairly well in one rabbit with the blood volume value determined by bleeding, and in ten human subjects gave values equal to 1/12 the body weight.

L. N. K.

Tetelbaum, A. G., Umanski, S. I., and Krynski, M. I.: The Influence of Physical Exertion on Venous Pressure in Health and in Cardiac Failure. *Wien. Arch. f. inn. Med.* 28: 121, 1935.

The authors used a direct venous pressure method. The needle was inserted in a cubital vein with the patient in the supine position. The exercise consisted in raising both legs 45 degrees above horizontal and maintaining this position for one minute with the knees straight. Venous pressure was estimated at frequent intervals after the legs were lowered. Eighteen subjects were studied: six normal persons, and six with moderate congestive heart failure, and six with severe congestive heart failure.

A rise of pressure of 30 to 50 mm. of saline with a rapid return to normal was observed after the exercise test in the six normal subjects. A higher rise (90 to 150 mm. and 105 to 160 mm.), was found respectively in the patients with moderate and those with severe heart failure. If the condition of the patient improved, the venous pressure rise approached the normal. If the condition of the patient became worse, the venous pressure changes became more abnormal. It was found that the venous pressure returned to the control level in 10 to 15 seconds after the exercise in normal persons and in from 35 to 70 seconds or longer in instances of cardiac failure. The duration of the venous pressure rise became shorter when the patient improved and became more prolonged when the patient's condition became worse. The authors consider this test of value in the study of cardiac failure.

W. B.

Henderson, Yandell, Oughterson, A. W., Greenburg, L. A., and Searle, C. P.: Muscle Tonus, Intramuscular Pressure and the Venopressor Mechanism. *Am. J. Physiol.* 114: 26, 1936.

A technic for determining pressure within a muscle is described and is used to show variations in tonus. This tonic intramuscular pressure was found to be a prime factor in the venous return of blood to the heart. By means of Rimpl's experiment, particularly on a sympathectomized animal, it is shown that tonic elasticity of tissues is sufficient to squeeze a considerable part of the blood in the body out through the veins under a pressure corresponding to a column of blood of 10 to 12 cm. The tonic tissue pressure throughout the body combined with the negative pressure in the thorax, which is largely dependent upon the tonus of the respiratory muscles, determines the "effective venous pressure" that in health assures the venous return. Failure of the circulation in illness and after physical injuries and surgical operations is largely due to diminution of general body tonus and stagnation of blood in the flaccid tissues.

E. A.

Wilson, Harwell, and Roome, Norman W.: The Effects of Constriction and Release of an Extremity; An Experimental Study of the Tourniquet. *Arch. Surg.* 32: 334, 1936.

Experiments were performed on nineteen dogs in an effort to study the effects of prolonged constriction of a limb. One hind limb was ligated by means of a rubber tourniquet for a period of from two to twenty hours under barbitol anesthesia and then released. Of these animals 69 per cent died in an average interval of twenty-five and three-fifths hours after release of the constrictor, while only 17 per cent of a control series died. No animal with a leg constricted for less than three hours died, while several animals with a leg constricted for a period in excess of six and one-half hours died.

It was thought that the reactive hyperemia of the constricted limb and the absorption of metabolites from the limb were probably responsible for the primary transient depression of the blood pressure when the constrictor was removed, but that the secondary and more serious fall of blood pressure was occasioned by swelling of the damaged extremity by transudation and the consequent diminution of the circulating blood volume. The absorption of the products of anaerobic bacteriolysis of the tissues is another possible factor in the lowering of the blood pressure, but no positive proof or denial of its importance can be adduced from the present experiment. Survival of the animal after prolonged constriction of a limb was obtained by amputation of the limb followed by transfusion of blood but not by transfusion or by amputation alone.

E. A.

Allen, E. V., and Brown, G. E.: Intermittent Pressure and Suction in the Treatment of Chronic Occlusive Arterial Disease. *J. A. M. A.* 105: 2029, 1935.

The authors present an evaluation of alternating negative and positive pressure in the treatment of obliterative arterial disease based on an analysis of cases in the literature and on their experience with 60 patients treated routinely with the pavaex apparatus developed by Herrmann and Reid. Thirty-two of the patients received sufficiently long periods of therapy to allow a preliminary estimate of the value of the method as used in the Mayo Clinic.

Allen and Brown are unable as yet to answer the question, "Do good results follow passive vascular exercise more frequently than other methods of treatment?" Their opinion is that "good results ordinarily follow changing environmental pressure treatment in cases in which good results could be expected from other measures and that when good results do not follow other measures, passive vascular exercise is usually valueless."

The pavaex method, however, "has been some contribution to the program of treatment." The greatest benefit observed by Allen and Brown is in the relief of the pain of ischemic neuritis.

L. H. H.

Symposium on the Autonomic Nervous System

Kuntz, A.: *The Autonomic Nervous System: Essential Anatomy.* J. A. M. A. 106: 345, 1936.

This presentation begins a symposium on the autonomic nervous system at the 1935 meeting of the American Medical Association. Its chief value lies in orienting one as to the basis for the various operations on the sympathetic nerves and ganglia.

Davis, L., and Pollock, L. J.: *The Rôle of the Autonomic Nervous System in the Production of Pain.* J. A. M. A. 106: 350, 1936.

Continuing the symposium, the authors discuss the chief theories of the relation of the autonomic system to pain. They conclude that the only proved contribution of the autonomic system to pain is in the utilization of the efferent fibers in certain of the referred types.

Brown, G. E.: *Clinical Tests of Function of the Autonomic Nervous System.* J. A. M. A. 106: 353, 1936.

As knowledge of the rôle played by the sympathetic and parasympathetic nervous systems increases, and therapeutic measures become more efficient, tests for the functional imbalance of these systems become essential. Brown has gathered together the important types of test so far evolved through which objective comparison of abnormal to normal function can be made.

Jackson, D. E.: *Essential Pharmacology of the Autonomic Nervous System.* J. A. M. A. 106: 357, 1936.

A brief consideration of the various drugs whose action on the autonomic system has been demonstrated.

Adson, A. W.: *Indications for Operations on the Sympathetic Nervous System.* J. A. M. A. 106: 360, 1936.

Adson closes the symposium on the autonomic nervous system by discussing the rationale of sympathetic surgery in such conditions as Raynaud's disease, scleroderma, rheumatoid arthritis, hyperhidrosis, essential hypertension, and certain types of pain. The presentation is an excellent summary of what may be expected in this new field in the hands of expert surgeons.

L. H. H.

Dotti, Enrico: *Experimental Studies of the Function of Lymphatic Vessels and Lymph Glands With X-ray After Subcutaneous Injection of Thorium Dioxide.* Fortschr. a. d. Geb. d. Röntgenstrahlen. 50: 615, 1934.

Roentgenological studies of lymph glands and lymphatic vessels of the legs of guinea pigs show that in diseases due to secondary infection of the lymph glands and vessels a less pronounced x-ray shadow is obtained after subcutaneous injection of thorium dioxide. It seems that the infection reacts on the reticulo-endothelial system, reducing its ability to retain the electronegative thorium dioxide and decreasing the permeability of the lymph vessels.

J. K.

Ernst, Curt: Localized Edemas in Human Beings. *Deutsche med. Wchnschr.* 61: 745, 1935.

Vasoneurotic and hypertonic (red hypertonic) patients are predisposed to developing local edemas in the skin and mucous membranes. Capillary examination of several hundred vasoneurotic and hypertonic patients showed characteristics of spastic-atonie capillaries. But the local edemas are not due only to the changes of the minute vessels; there are also present typical changes in the skin tissue. The elasticity of the skin is decreased; measured with an elastometer (Schade), it showed a decrease in elasticity from 14 per cent to 38 per cent. Intracutaneous injection of 1:1,000,000 solution of morphine gave in this type of patients a more pronounced reaction, more lasting and larger wheals and redness, suggesting an increased amount of fluid in the skin. Intracutaneous histamine injection showed increased capillary permeability.

Vasoneurotic individuals are predisposed to certain diseases such as gastric ulcer, red hypertension, Raynaud's disease, ulcerative colitis, Ménière's disease, and certain types of asthma, cystitis, and glaucoma.

J. K.

Behnke, Albert R., Shaw, Louis A., Messer, Anne C., Thomson, Robert M., and Motley, E. Preble: The Circulatory and Respiratory Disturbances of Acute Compressed Air Illness and the Administration of Oxygen as a Therapeutic Measure. *Am. J. Physiol.* 114: 526, 1936.

Nitrogen emboli were produced in the blood of anesthetized dogs by rapid decompression from air compressed to 65 pound gauge pressure for 105 minutes. Rapid breathing, temporary rise followed by a fall in the blood pressure, retarded pulse rate, oxygen unsaturation of the arterial blood, and a marked increase in the arteriovenous difference were noted. The rapid breathing and unsaturation of the arterial blood are attributed to embolic blockage of the pulmonary circulation, and the fall in blood pressure and increased arteriovenous difference are attributed to embolic injury to the nerve tissue which controls circulation.

E. A.

Smith, Fred M., Rathe, H. W., and Paul, W. D.: Theophylline in the Treatment of Disease of the Coronary Arteries. *Arch. Int. Med.* 56: 1250, 1936.

It is important that measures be directed toward the restoration and maintenance of an efficient coronary circulation in the treatment of disease of the coronary arteries. The preparations of theophylline have a marked dilating action on the coronary vessels in the experimental animal, and clinical experience has demonstrated that they are valuable therapeutic agents in the treatment of disease of the coronary arteries, regardless of whether the cardiac disability is expressed by congestive failure, paroxysmal dyspnea, angina on effort, or occlusion of the coronary arteries. Questionable results and failures are encountered, but this is to be expected in the more advanced forms of the disease. Theophylline should be prescribed as soon as the diagnosis of disease of the coronary arteries is established, and its administration should be continued for a long period, in order to insure the maximum benefit from the medication. It should be remembered, however, that this constitutes only one measure in the treatment and, except for experimental purposes, should not be employed to the exclusion of other established means of restoring the cardiac function.

AUTHOR.

Book Reviews

THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE PERIPHERAL ARTERIES. By Saul S. Samuels, A.M., M.D., New York, 1936, Oxford University Press.

This work is of undoubted value because it represents a strong brief for the conservative treatment of peripheral arterial diseases. In it the author has set forth evidence in the form of case reports, both singly and grouped, of patients suffering from thromboangiitis obliterans and arteriosclerosis obliterans, treated by conservative methods with excellent results.

The title of this volume, however, is somewhat misleading. Instead of a well-balanced presentation of the diseases of the peripheral arteries, in which space is allotted to each group according to its relative importance, we find the following distribution: In a volume of 254 pages, 148 pages are devoted to thromboangiitis obliterans, 48 pages to arteriosclerosis obliterans, 5 pages to Raynaud's disease, and 2 pages each to erythromelalgia and essential thrombophilia. Syphilitic arteritis, embolism, acrocyanosis, scleroderma, and polycythemia with vascular complications are merely mentioned, and there is no reference to lead sclerosis or rheumatic arteritis. Most of the diseases are mentioned for the purpose of differential diagnosis only. The book is really a monograph on thromboangiitis obliterans, with a discussion of arteriosclerosis obliterans included.

The description of thromboangiitis obliterans, a disease with which the author has had considerable experience, is very good. When it comes to treatment, however, the author merely presents his form of therapy, and condemns either by direct statement or by faint praise other recognized forms. All workers in this field will agree with his demand for complete abstinence from smoking, but the attitude that saline, given intravenously, is the one acceptable form of therapy to stimulate the circulation will be questioned by those who use citrate and by the large number of workers who have found typhoid vaccine, intravenously administered, to be the most satisfactory form of therapy for this purpose. His approach, moreover, shows a lack of understanding of the correct use of typhoid vaccine. The reviewer could find no mention of hepatitis or other complications which sometimes occur with saline therapy.

Although Raynaud's disease may have been relatively rare in Dr. Samuel's clinic, other vascular clinics are finding it very frequently, in varying degrees of severity. A more detailed consideration should therefore be given to it in a volume presuming to cover the entire field of peripheral arterial diseases, even though it is recognized that the defective mechanism may be in the nervous supply to the arterial system.

If this volume, in spite of its defects, will encourage physicians to have patience and courage enough to be conservative in the treatment of arterial disease, many extremities and, indeed, lives will be saved each year.

I. S. W.

LA TENSION MEDIANA DINAMICA: ESTUDIO CRITICO (CLINICO Y EXPERIMENTAL). By Dr. Angel Cammaroto. Buenos Aires, 1935, El Ateneo, 169 pp.

Dr. Cammaroto in this work, the thesis for his doctorate, presents the results of a detailed study of median dynamic tension, a subject which is of rather limited interest. The volume is generously illustrated and well printed on good paper.

After chapters on historical aspects of the subject, definition and method of determining the median arterial tension, the normal tension and its variations, he considers the median dynamic tension in relation to aortic insufficiency, arterial hypertension, hypotension, bradycardia, aneurysms, and hyperthyroidism. He then discusses solitary median hypertension, reviews the subject critically, and presents his conclusions which are as follows: The median tension varies within wide limits as do the systolic and diastolic pressures. Within the space of a few minutes it can vary rapidly. It appears to be related, at least in part, to vasomotor innervation. It is usually related to the extremes of blood pressure even when its relation to the diastolic pressure is more evident. It does not appear to be of particular interest in prognosis or in diagnosis. Median hypertension was not found as an isolated sphygmomanometric observation. The results obtained with the compensating manometer lack exactitude, and hence experimental contributions must be regarded as of doubtful value.

E. H.

ÉTUDE ANATOMO-RADIOLOGIQUE DE L'APPAREIL CIRCULATOIRE PAR OPACIFICATION POST-MORTEM: INTÉRÊT, TECHNIQUE, ET VALEUR DE CETTE MÉTHODE. By Pierre Hebert. Paris, 1935, Librairie E. Le François, 75 pp. with 13 figures.

ANATOMIE RADIOLOGIQUE DES CAVITÉS CARDIAQUES ET DU PÉDICULE VASCULAIRE. By R. Heim de Balzac. (Reprinted from *Leçons de Cardiologie Faites à l'Hôpital Broussais*.) Paris, 1935, Gaston Doin & Cie., 24 pp. and 23 figures.

These two brief studies are based on a large amount of painstaking work undertaken in order to establish more accurate knowledge of the x-ray appearance of the heart and the great vessels. The studies were made on the cadaver by means of the injection of an opaque material into the right and left sides of the heart separately, followed by careful radiological study. This method allows the visualization of the two sides of the heart separately but is not intended for or suitable for clinical use.

E. H.

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Original Communications

INTERMITTENT CLAUDICATION STUDIED BY A GRAPHIC METHOD*

L. H. HITZROT, M.D., M. NAIDE, M.D., AND E. M. LANDIS, M.D.
PHILADELPHIA, PA.

ALTHOUGH pain is the striking subjective phenomenon of intermittent claudication and the criterion by which the severity of the condition is usually judged, fatigue of the contracting muscles precedes it. The early loss of contractile power or amplitude of contraction in muscle deprived of adequate blood supply is an objective phenomenon which can be recorded graphically. The ergograph¹⁻³ has demonstrated the theoretical and practical value of such graphic records of muscular fatigue.

The contractions depend upon the volition of the patient, and the ergograph records are to that extent subjective. The human calf muscles can, however, be made to contract involuntarily by electrical stimulation. The apparatus to be described was designed by one of us (E.M.L.) for the purposes of (1) producing involuntary contractions of the calf muscles by faradic stimulation at set intervals and (2) recording the development of fatigue graphically under standard conditions of stimulus and load. In this preliminary account are presented studies on normal subjects and on patients with peripheral vascular disease. Illustrative records indicate the usefulness of the procedure in estimating objectively the degree of claudication and in recording graphically changes occurring in the course of treatment.

APPARATUS

The apparatus for recording the development of fatigue in the muscles of the leg during stimulation is shown in lateral view by Fig. 1A and in end view by 1B. The base (A) consists of a board 33 inches long and 12 inches wide, extending from a point approximately 8 inches above the knee to a point about 10 inches below the sole of the foot. A vertical footboard (B), measuring 11.5 inches by 10 inches, is attached to this base by means of a hinge (C) constructed with its center of rotation approximately opposite to that of the ankle joint so that the foot may be

*From the Peripheral Vascular Section of the Roblnette Foundation, Hospital of the University of Pennsylvania.

extended on the leg normally without undue strain. This footboard bears in the center a support for the heel (*D*) and two adjustable straps, one (*E*) passing over the ankle joint, the other (*F*) holding the instep lightly just proximal to the toes.

The footboard is held vertically against an adjustable stop (*G*) by two spiral springs (*H*) and several layers of sponge rubber (*I*) compressed slightly in the space between the lower edge of the footboard and the horizontal base. The force required to displace the footboard forward can be increased (a) by stretching one or both spiral springs more tightly on hooks (*J*) attached to each side of the base, or (b) by increasing the amount of sponge rubber under the edge of the footboard. In general it was found convenient to use six thicknesses of $\frac{1}{4}$ inch sponge rubber bandage with the springs only slightly stretched, i.e., in the first hook as shown in Fig. 1A. This tension resists contraction adequately and serves to bring the foot promptly back to the original vertical position as soon as muscular relaxation permits.

The calf muscles are stimulated through adjustable electrodes (*K*) applied one on each side of the leg in the position shown in Fig. 1A. Each electrode, measuring *in toto* 4 inches by $2\frac{1}{2}$ inches with a thickness of $\frac{3}{4}$ inch, encloses a sheet of $\frac{1}{16}$ inch lead soldered firmly to the upright (*L*). Since the muscles of the calf change their contour conspicuously during contraction, the inner surface of each electrode must be highly resilient in order to maintain contact with the skin uninterruptedly. Hence a layer of $\frac{1}{4}$ inch sponge rubber bandage was placed inside each lead plate and held in position by a series of flexible lead strips, $\frac{1}{32}$ inch thick and $\frac{1}{4}$ inch wide, placed closely side by side to cover the entire inner surface of the sponge rubber. The ends of these strips were bent round the ends of the heavy lead plates and soldered to the outer surface of the plates, the whole electrode being enclosed in a gauze envelope. The sponge rubber, while forcing the gauze and each thin lead strip individually against the skin, still does not interfere with conduction of current. Each electrode is insulated by means of hard rubber from the holder (*M*) and is connected to the stimulating device described below by a separate wire (*N*). In preparing for an observation, the two electrodes are bent to conform to the shape of the calf muscles, soaked thoroughly in 80 per cent alcohol, and then fixed in place. Two thumbscrews (*O*) on the holder (*M*) are tightened so that the electrodes are held constantly and firmly against the skin.

A vertical iron rod (*P*) beyond the footboard supports a telechron motor (*Q*) which, through appropriate gears, propels a strip of adding machine paper (*R*) at the rate of 2 millimeters per second over a small drum (*S*) and, in addition, controls the duration and frequency of the electrical stimuli applied to the muscles of the leg through the electrode described above.

The rate of stimulation is controlled by the rotation of a notched bakelite disk (*T*) which keeps open the switch (*U*) except when one of the notches passes over the roller (*V*). The bakelite disk makes a complete rotation in four seconds. The disk shown in Fig. 1B contains four notches, and stimuli are therefore applied to the leg muscles once per second. Another disk containing two notches is used for stimulating every two seconds, and a third disk with one notch for stimulating every four seconds. The duration of each stimulus can be adjusted by a small vertical screw between the vacuum switch (*U*) and the roller (*V*). In these studies a stimulus of 0.07 second duration was used.

The vacuum switch (*U*) is connected in series with the secondary of an induction coil and with a manually operated switch which is used to interrupt the stimulating current completely during rest periods or when readjustments of the intensity of stimulation are necessary.

Since a tetanic contraction of short duration is desired, a faradic current from the secondary of an induction coil is used. Various types of mechanical induction apparatus and various rates of faradization were tried. It was found finally that

single phase 60 cycle, 110 volt alternating current in the primary circuit provided constant and effective stimuli. The intensity of contraction is varied by changing the amperage in the primary circuit. Appropriate resistances (e.g., a bank of lamps in parallel) are used to increase the amperage by 0.1 steps from 0.5 to 5.0

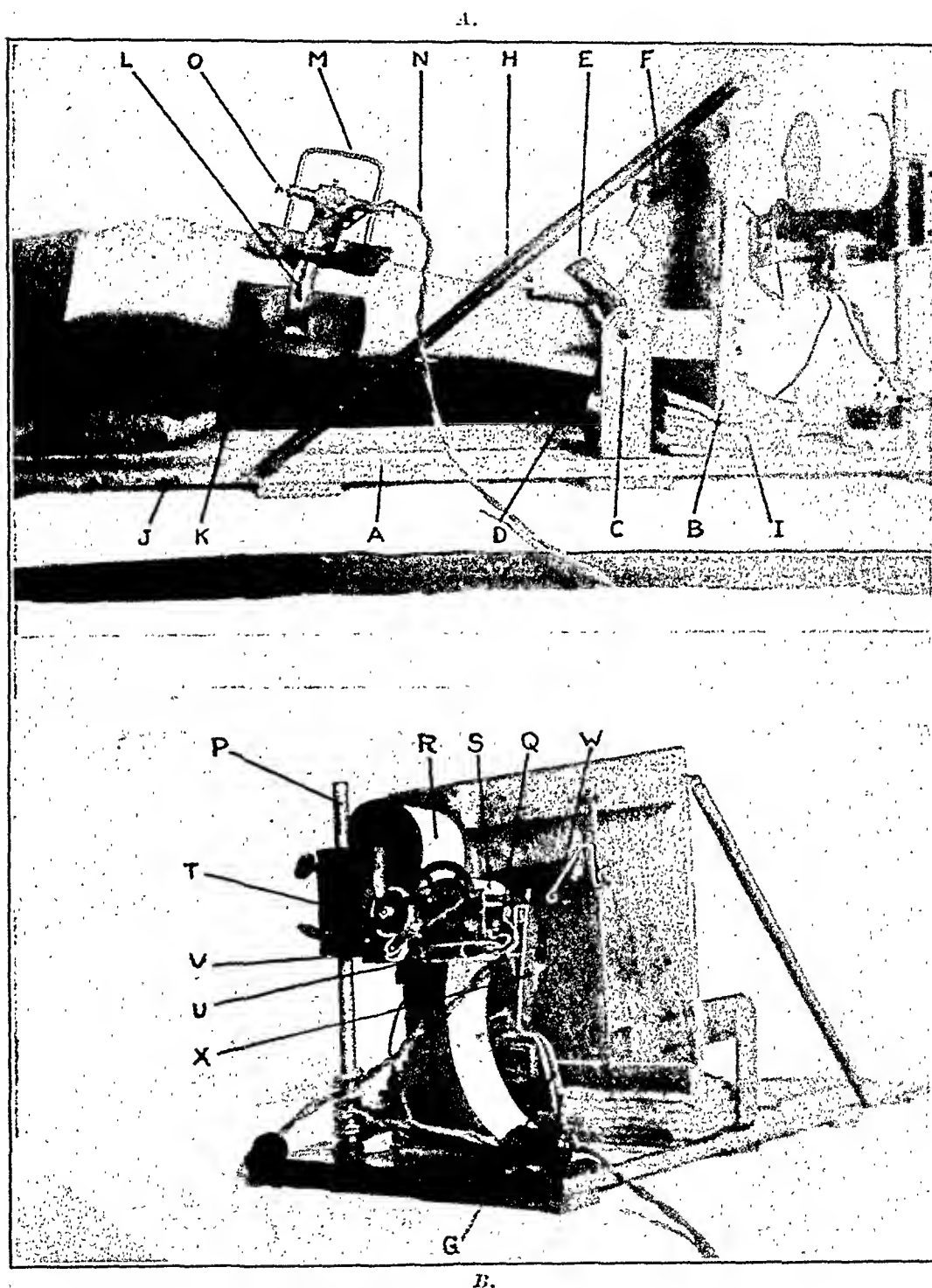


Fig. 1.—A, side and B, end-oblique views of apparatus for recording fatigue of calf muscles. For description see text.

amperes, the exact amount being read on an ammeter in series with the primary of the induction coil. One important precaution is to be observed carefully. The manual switch in the secondary circuit is *always turned off* before the amperage of

the primary circuit is changed, since otherwise the induced current temporarily stimulates undesirably painful and intense tetanus of the calf muscles.

During stimulation, contraction of the calf muscles extends the foot and the sole is pressed against the footboard. A metal rod (*W*) transmits any movement of the footboard to an ink writing pen (hidden behind the switch in Fig. 1*B*) mounted on a lever (*X*) held against the paper by a light spring. The excursion recorded by the pen is approximately equal to the excursion of the ball of the foot. The relation between excursion and the work performed against the resistance of steel springs and sponge rubber arranged as in Fig. 1 is as follows:

EXCURSION IN MILLIMETERS	WORK IN FOOT POUNDS*
4.0	0.69
10.0	2.50
20.0	6.40
30.0	13.65

*We are indebted to Mr. A. Rawson, of the Johnson Foundation, University of Pennsylvania Hospital, for this determination.

METHODS

The subject, after resting at least fifteen minutes, assumes a semi-reclining position on an examining table with a back support at an angle of 45 degrees. The foot is strapped in the holder, and the electrodes are placed as shown in Fig. 1. Stimuli are applied to the calf muscles at the rate of one in four seconds and the amperage, initially 0.5, is increased gradually until the amplitude of contraction recorded by the pen is between 18 and 25 mm.

The procedure adopted as routine was arranged to reveal (a) the effects of varying rates of stimulation, (b) the rate of recovery after different grades of fatigue had been produced, and (c) the cumulative effects of frequently repeated mild fatigue. The routine test required eighteen minutes for each leg and was arranged as follows:

1. Stimulation, once per four seconds, for two minutes.
2. Rest, one minute.
3. Stimulation, once per two seconds, for two minutes.
4. Rest, one minute.
5. Stimulation, once per second, for two minutes.
6. Rest, three minutes (renew alcohol on electrodes).
7. Stimulation, once per second, for one minute.
8. Rest, thirty seconds.
9. Etc., repeating parts 7 and 8 for a total of five short contraction and rest periods.

The long strip of graphic record can be cut into convenient lengths and mounted for easier analysis and filing.

OBSERVATIONS

A. Normal Subjects

A complete original record obtained from a normal subject is shown in Fig. 2. The amplitude of contraction did not diminish significantly until stimuli entered at the rate of one per second. The subject did not,

in the course of the test, experience fatigue or pain, though objective evidence of slightly reduced muscular efficiency was present.

The fatigue record obtained from a normal subject after blood flow in the extremity was stopped completely is shown in Fig. 3. A wide pneumatic cuff, encircling the thigh just above the knee, was inflated suddenly to 200 mm. of mercury just before beginning the usual routine

FATIGUE RECORD — CIRCULATION NORMAL

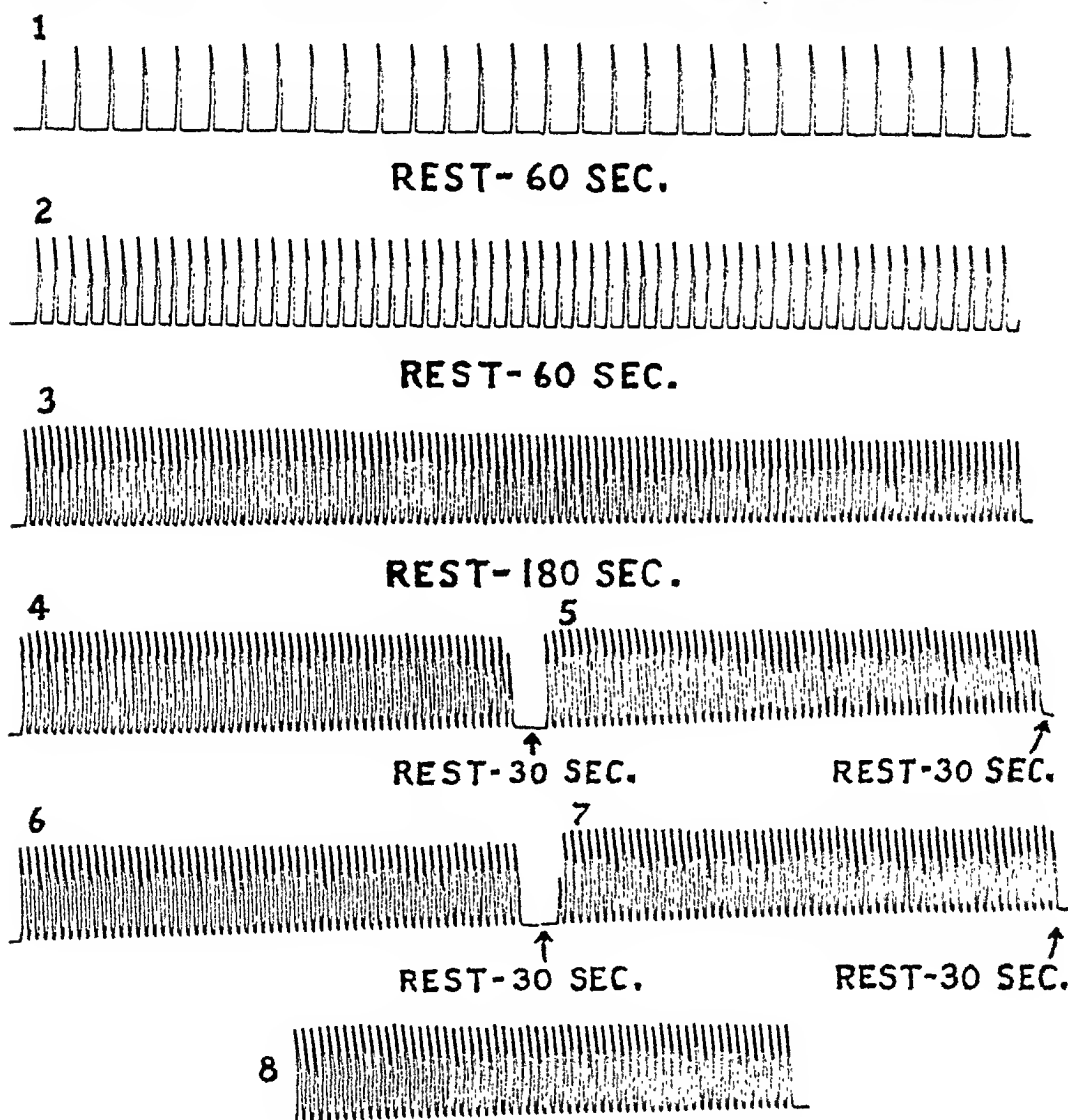


Fig. 2.—Fatigue record of normal subject.

stimulation (marked by arrow on record 1, upper part Fig. 3). The amplitude of contraction diminished measurably in the latter part of the first period though contractions were induced only once in four seconds. There was no recovery during the succeeding rest period. A few contractions at the rate of one in two seconds produced pain which increased steadily. The amplitude of contraction diminished conspicuously, and the reactions of the calf muscles became extremely sluggish,

both in contraction and in relaxation. The subsequent rest period again brought no recovery, and a few contractions at the rate of one per second developed intolerable pain. The cuff was released; during continued stimulation pain disappeared within twenty seconds and the

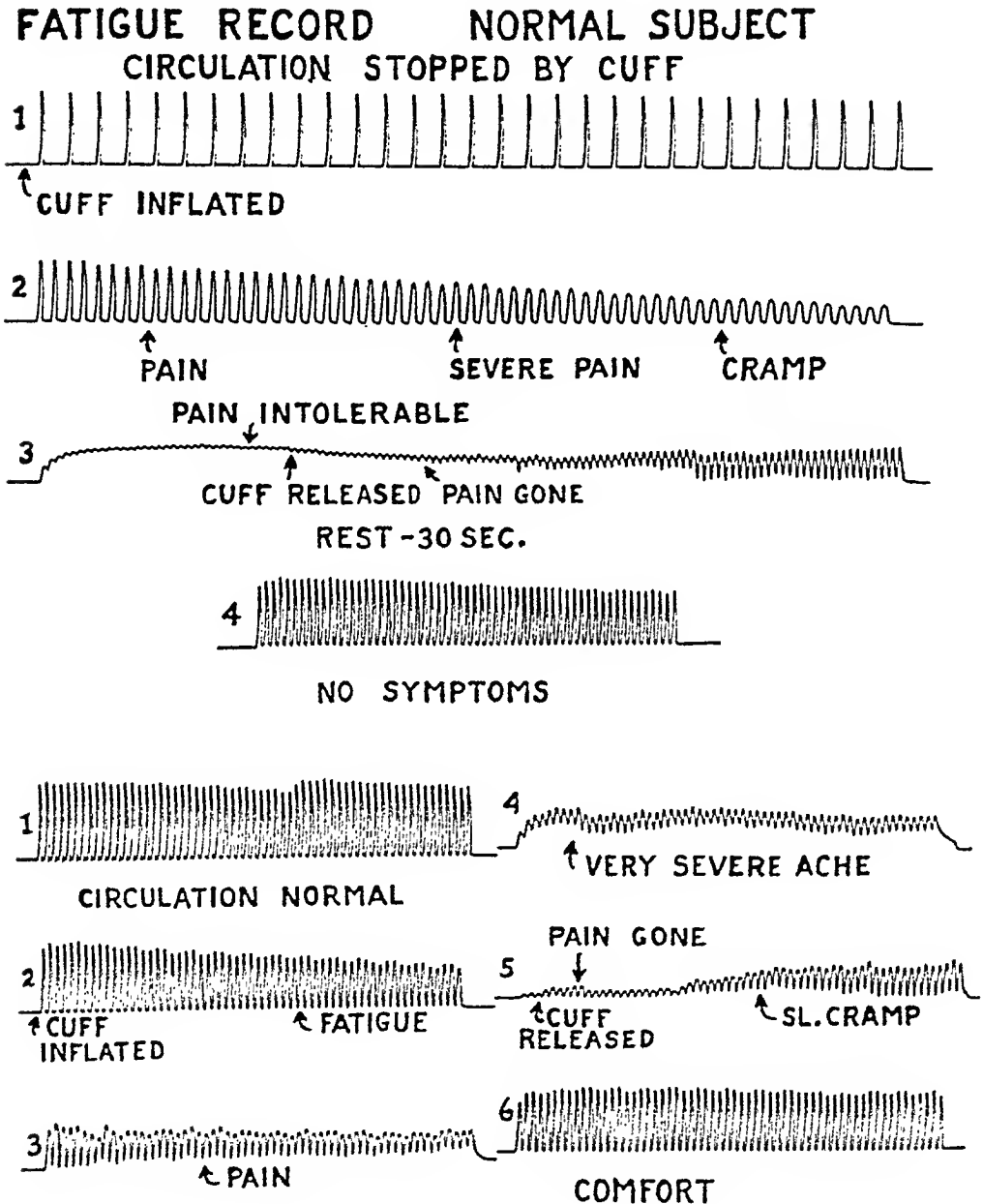


Fig. 3.—Fatigue record of normal subject after blood flow to the leg was arrested. Upper section (4 records) to be compared with records 1 to 4 inclusive, of Fig. 2. Lower section (6 records) to be compared with records 4 to 8, inclusive, of Fig. 2.

amplitude of contraction steadily increased. More complete recovery is shown in record 4 (upper part of Fig. 3), after the usual rest period. The lower section of Fig. 3, for comparison with lower Fig. 2, shows the effect of arresting blood flow on a series of contractions at the rate of one per second for periods of one minute with rest intervals of thirty

seconds. Again amplitude diminished considerably before pain appeared; contraction and relaxation became sluggish; and the rest periods did not produce the recovery observed when blood flow was free.

1. *Routine Fatigue Curves of Normal Subjects.*—The original records in Figs. 2 and 3 illustrate the changes produced when blood flow to the limb is completely obstructed, a condition far more severe than that to be expected in patients with intermittent claudication. To expedite plotting of results and more precise quantitative comparison, "fatigue curves" were prepared from the original records (Fig. 4).

The average height of the first five and last five strokes of each stimulation period were measured in millimeters. These amplitudes (in milli-

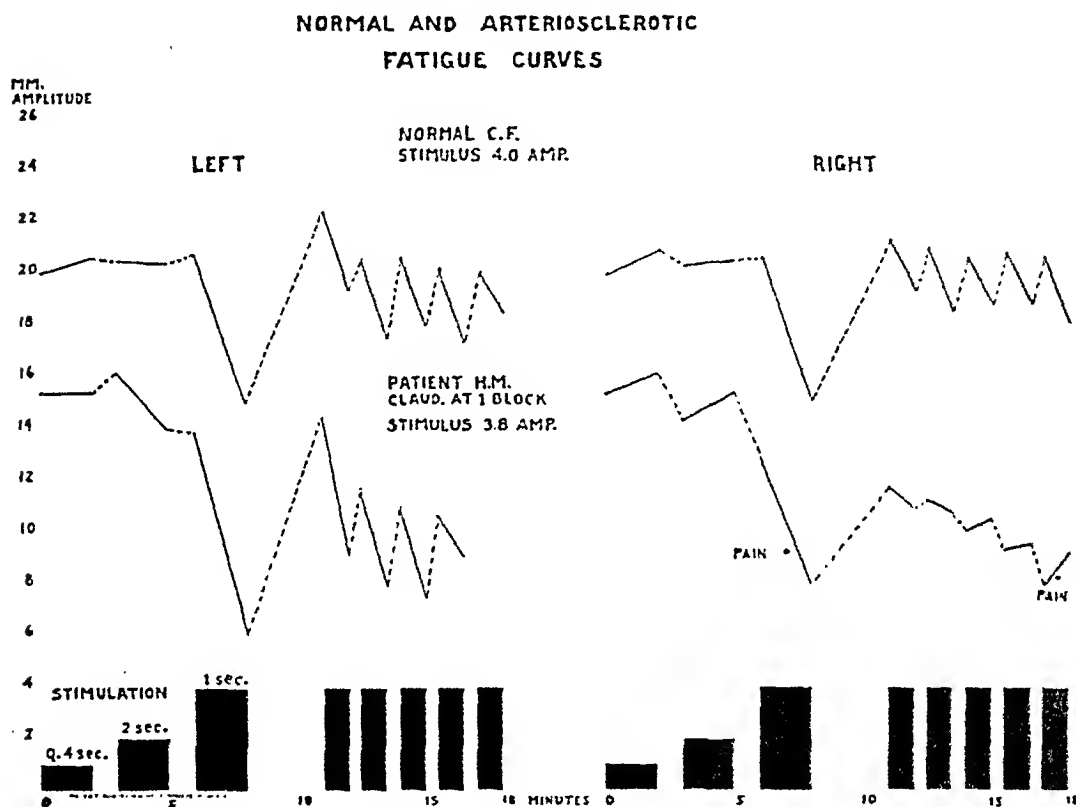


Fig. 4.—Examples of the contrasting curves obtained in a normal subject and a patient with intermittent claudication in the right leg. The amplitude of contraction at the beginning and end of each stimulus period has been plotted as described in the text. The gain or loss of amplitude during stimulation is indicated by the solid lines; the rest period by broken lines. The shaded areas below indicate the stimulation.

meters) plotted as abscissae against time in minutes as ordinates summarized the significant changes occurring during the entire test. In Fig. 4 the upper lines show such fatigue curves for a normal subject; the lower lines show, for contrast, the fatigue curves of a patient with claudication in the right leg. The solid portions of each curve represent stimulation periods; the shaded areas below indicate the rate of stimulation. The dotted portions of each curve represent rest periods.

The upper (normal) fatigue curve in Fig. 4 indicates that a current of 4.0 amperes produced a contraction amplitude of 20 mm. This initial

2. During slow stimulation amplitude remained constant. Rapid stimulation gradually diminished the amplitude of contraction by 50 and 20 per cent in the two- and one-minute periods, respectively.

3. Whatever fatigue developed during periods of contraction disappeared during the stipulated rest periods, the amplitude of contraction returning almost completely to the initial amplitude after each brief rest.

4. Age, per se, did not affect the record. In this normal group those of sixty years or over produced curves similar to those of younger individuals.

5. General weakness after long confinement to bed produced for a given strength of stimulus, lower amplitudes and mild sensations of fatigue, but neither the claudication pain nor the rapid drop in amplitude which is characteristic of vascular disease.

2. Fatigue Curves of Normal Subjects Under Experimental Conditions.

—*Complete obstruction of blood flow* (Fig. 3) produced fatigue or pain with loss of 7 per cent in amplitude even during slow stimulation (once in four seconds). In the succeeding rest period, there was no recovery. Stimulation at the rate of once in two seconds produced severe symptoms, and amplitude was reduced by 67 per cent of the initial value—again without recovery in the succeeding rest period. Intolerable pain developed after a few barely measurable contractions at the rate of once per second, and it was impossible to continue the test. Symptoms and signs of muscular fatigue disappeared shortly after blood flow was resumed.

Venous congestion by a pneumatic cuff inflated to a pressure of 40 to 60 mm. of mercury favored slightly the development of fatigue as measured subjectively and objectively. The changes were barely measurable and far less than those observed with completely obstructed blood flow. With cuff pressures of 80 to 120 mm. of mercury the amplitude of contraction was diminished as much as 60 per cent in the standard stimulation period. Two subjects suffered discomfort and one severe pain. The effects of marked venous congestion were roughly similar to those of mild peripheral vascular disease in patients.

Peripheral vasodilatation in normal individuals produced little or no change in the fatigue curve. Peripheral vasoconstriction was induced in normal subjects by exposure to an environmental temperature of 20-21° C. When digital temperatures reached 23° C., complete tracings were made. Vasodilatation was then induced by enclosing the forearms in electric heating pads and the body in blankets until skin temperature of the lower extremities rose above 30.5° C. Fatigue curves taken in this period showed rather less diminution in amplitude with exercise, but the changes observed were no greater than those that might be accounted for by a rest period of equal duration.

B. Fatigue Curves of Patients With Peripheral Vascular Disease

In twenty patients, seventeen men and three women, whose ages ranged between forty and seventy years (average fifty-one), the fatigue curves varied with the severity of the arterial deficiency. All differed from the curves obtained from normal subjects under comparable external conditions. These patients had intermittent claudication: fourteen because of arteriosclerosis, five because of thrombo-angiitis obliterans, while one fell in the group in which clinical differentiation between these two conditions is impossible.

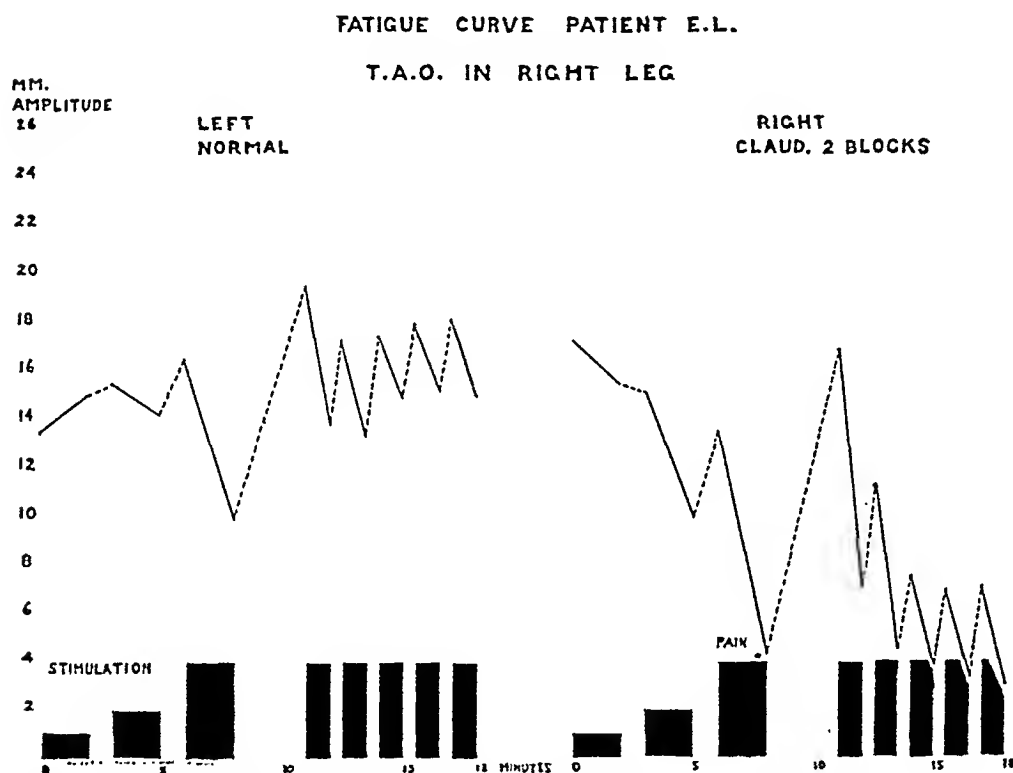


Fig. 6.—Comparative results in the two extremities of a patient with unilateral peripheral vascular disease.

The fatigue curves of a patient with arteriosclerosis are shown in Fig. 4 for comparison with the usual normal curve. This patient had claudication in the right leg only, but the responses of both legs were abnormal. A current of 3.8 amperes produced a contraction amplitude of 15 mm. This initial amplitude was not maintained owing to cumulative fatigue in the contraction period (solid lines) and cumulative incomplete recovery (dotted lines) during the rest periods. The objective changes were quantitatively greater in the leg presenting clinical evidence of ischemia.

A completely normal curve in one extremity may be associated with conspicuously reduced functional power in the other extremity, as shown in Fig. 6, which presents the fatigue curves of a patient with thrombo-

angiitis obliterans. Symptoms, including claudication upon walking two blocks, were limited to the right leg, as was also objective evidence of vascular deficiency.

The composite fatigue curves of twenty patients with peripheral vascular disease are shown in Fig. 7. The results on the more involved leg of each patient have been grouped together for comparison with the composite fatigue curves of normal subjects. As compared with the normal, records taken in patients with peripheral vascular disease present singly and collectively the following features:

1. The same intensity of stimulation (in amperes) generally produces a lower amplitude of contraction than in the normal subject. So far as

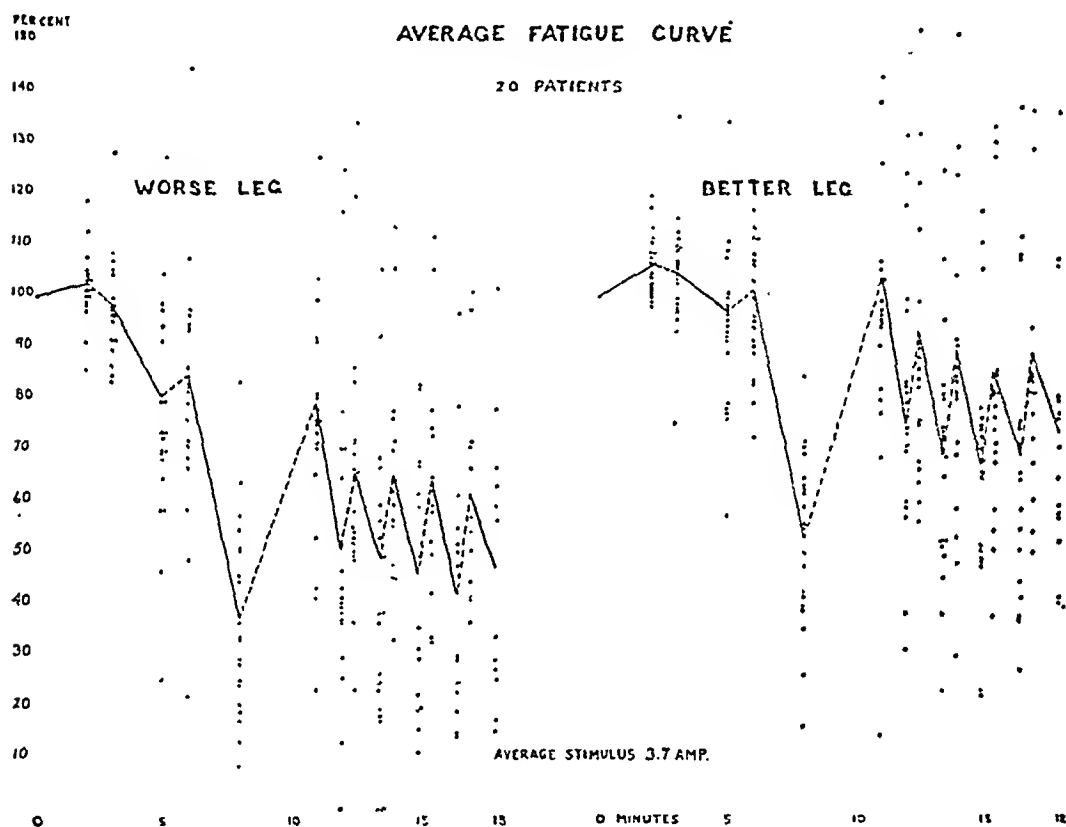


Fig. 7.—Composite curves plotted as described for Fig. 5 to show the lack of recovery of muscle power in patients with arterial disease.

can be judged at present, this difference cannot be attributed either to general weakness or to the smaller calf muscles usually found in patients with peripheral vascular disease.

2. The amplitude of contraction begins to diminish earlier and declines more rapidly in the course of the standard series of contractions.

3. In the routine rest periods muscle power recovers decidedly less completely so that the fatigue curves show, as a whole, a more or less conspicuous slope downward as the test proceeds.

4. This diminution in amplitude is associated with sensations of fatigue and claudication pain. The latter may be so severe that the test cannot be completed. When vascular occlusion has occurred recently,

the severity of fatigue and pain resembles very closely that observed in normal subjects whose blood flow to the calf muscles is completely interrupted by a pneumatic cuff.

C. Fatigue Curves of Patients With Peripheral Vascular Disease in the Course of Treatment

As clinical improvement occurs in the course of therapy, pathological fatigue curves should gradually return toward the normal form if that improvement is due to restoration of circulation. Two charts (Figs. 8 and 9) are included to indicate the possible clinical usefulness of the procedure in this regard.

Figure 8 shows two fatigue curves made in the course of recovery after sudden deprivation of major blood supply by thrombosis. In the earlier test it was impossible to complete the procedure owing to the development of severe pain associated with complete loss of contractile

PATIENT W.W.
ARTERIAL OCCLUSION (THROMBOSIS)
TREATED BY SUCTION-PRESSURE

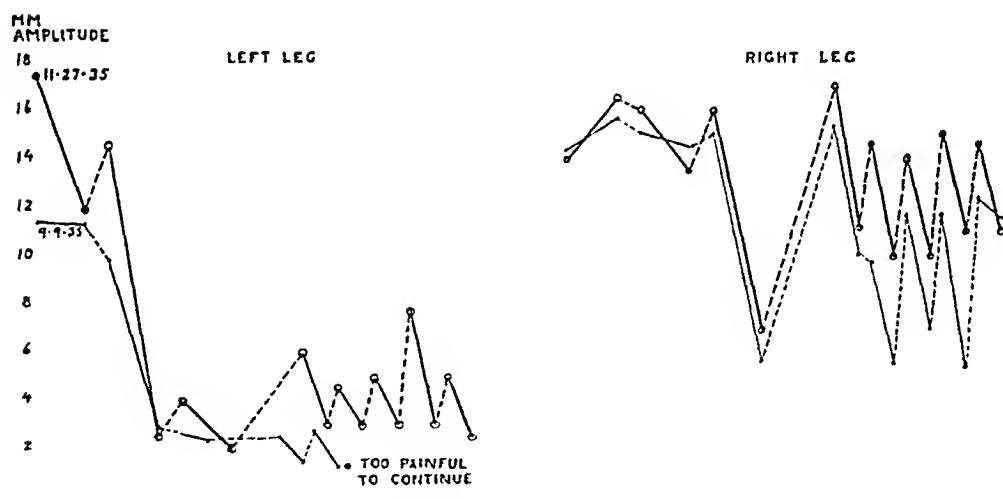


Fig. 8.—Effect of bed rest and thirty-seven hours of suction pressure to left leg in acute ischemia of the extremity. Light lines, curve before treatment; heavy lines, after clinical improvement was definite.

power. Later, contractile power was still conspicuously reduced, but the recovery during each rest period was much increased, and the test could be completed without pain. In the interim the patient had been treated by bed rest and thirty-seven hours of suction and pressure therapy for the left leg. Figure 9 exemplifies a series of curves being assembled in a study of the effects of tissue extract injections on intermittent claudication. Between the two tests shown, the patient received a total of twenty injections in a period of ten weeks with gratifying relief of claudication. A short period of suction and pressure therapy had produced only very slight benefit.

DISCUSSION

The manifestations of intermittent claudication are often entirely subjective and, like the angina of effort, they are open to misinterpretation by the patient or his physician. An objective test of circulation in the calf muscles is most needed when claudication is suspected in a patient in or near the arteriosclerotic age who still retains normal foot color, vasodilator responses, peripheral pulses, and roentgenogram. Moreover, pain in the lower extremities brought on by activity may be due to faulty mechanism of an orthopedic type, to neurological disorders, to anemia or to neurosis. It is in these patients that an objective test is valuable for diagnostic purposes. When the history of intermittent claudication is completely typical and when obvious evidence of arterio-

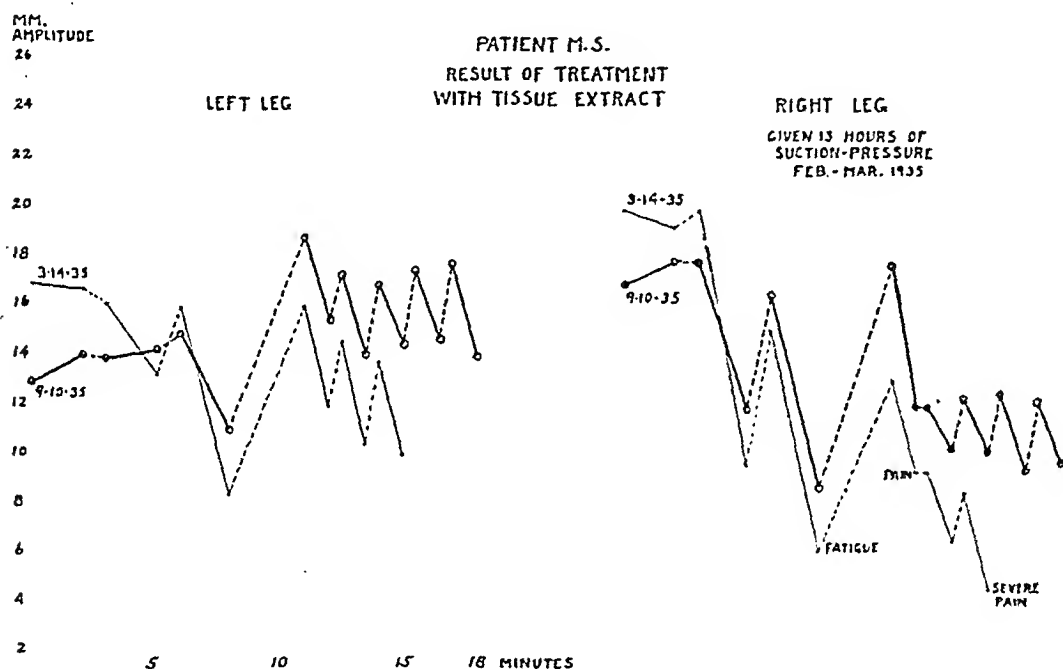


Fig. 9.—Example of graphic record of improvement with treatment in a case of arteriosclerosis. Twenty injections of tissue extract were given between the dates indicated.

sclerosis or other arterial disease is present, refined objective tests are not necessary for proper diagnosis.

During treatment, the effectiveness of therapy is usually estimated from the patient's own observations during uncontrolled exercise or during standard pacing such as described by Barker, Brown, and Roth.⁴ The apparatus and the method presented above permit the production and objective recording of the fatigue of intermittent claudication, which so far has been described for the most part in terms of subjective sensation. It should be possible to observe more accurately than heretofore the effects of peripheral vascular disease on the function of the calf muscles, as well as the effects of therapy. It must be remembered, however, that muscle weakness or atrophy due to other than vascular causes,

may also produce abnormal curves. History, routine examination, and the form of the tracing should prevent difficulties in differential diagnosis.

The passage of faradic current through the skin produces a peculiar sensation best described, perhaps, by the terms "tingling" or "thrill." Under proper conditions there should be little or no pain. Of the fifty patients of all types so far tested only one, a highly neurotic woman, experienced such discomfort at the electrodes that the test had to be discontinued. A certain amount of cooperation on the part of the patient is necessary for obtaining good records; the muscles must be relaxed, not voluntarily contracted owing to tension or apprehension. In excitable individuals reassurance and slow increase of amperage will favor complete relaxation.

The electrodes should not be placed too near the peroneal or anterior tibial group of muscles. If the calf muscles and their antagonists are both stimulated, fatigue occurs earlier than would otherwise be the case owing to the double load against which the calf muscles must contract. Though somewhat time-consuming the test is relatively simple and can be carried out completely by a trained technician. The objective character of the results and their graphic recording compensate for the additional time and effort involved.

SUMMARY

A method of recording graphically the fatigue of the muscles involved in intermittent claudication is described. The calf muscles are stimulated faradically at selected rates for brief periods, without depending upon the volition of the subject. Fixed periods of stimulation, alternating with short rest periods, allow the measuring under standard conditions not only of the rate of fatigue, but also of the rate of recovery.

A series of normal fatigue curves is compared with a series of curves obtained from patients with peripheral vascular disease. Certain typical changes are related to deficient arterial blood supply.

It is suggested that the method may aid in detecting vascular insufficiency involving the calf muscles in questionable cases and that it may assist in estimating objectively the efficacy of therapeutic measures.

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THE INEFFECTIVENESS OF DRUGS UPON COLLATERAL FLOW AFTER EXPERIMENTAL CORONARY OCCLUSION IN DOGS*†

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OPINION is still at variance as to the completeness of the ischemia which follows total occlusion of a large coronary branch and as to the chances of promptly starting sufficient collateral blood flow by use of drugs to prevent contractile failure or to minimize the succeeding necrosis and fibrosis. A complete answer cannot be expected from experiments designed to test the effects of drugs on coronary outflow or inflow; the problem is a composite one, involving an understanding of altered hemodynamics no less than the vascular actions that particular drugs may have. In studies utilizing the perfused heart, the dynamics of ventricular contraction are decidedly abnormal; the nervous supply to the vessels is severed; and doses are frequently employed that are precluded for human use. In studying the coronary sinus flow from intact hearts, these difficulties are avoided, but the danger exists, despite apparent evidence to the contrary, that the same aliquot part of the total coronary flow is not always drained away. Consequently the magnitude of, and perhaps even the directional changes in, flow may not be correctly indicated. While such difficulties appear to have been overcome by measurements of mean total inflow in specially designed perfused preparations or by application of Rein's thermostromuhr to an unopened coronary vessel, it must be evident that effects of drugs on coronary flow so established necessarily apply to changes of flow in distributing branches of the vessel studied and give no information as to improvement or impairment of collateral flow to an ischemic area.

Suppose as diagrammatized in Fig. 1, vessel *A* supplies an area of the myocardium denoted by *A'* and connects through collaterals *C* with another vessel, *B*. Following occlusion of vessel *A*, the only source from which area *A'* could receive blood would be through collateral channels schematically indicated at *C*. This single diagrammatic connection may be allowed to represent either intercoronary, extracoronary, or arterioventricular communications. It should be obvious that most of our knowledge regarding the pharmacological action of drugs applies to effects produced on branches of vessel *A* and gives no information regarding changes in caliber of collateral vessels represented by *C*.

The only attempt to evaluate such actions are the recent studies of Fowler, Hurewitz, and Smith,¹ who observed the changes in color of an

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ischemic area and compared the size of infarcts following ligation of a coronary branch in animals left untreated with those to whom various drugs had been administered. The problem has apparently not been approached from hemodynamic angles owing to the fact that no criterion of changes in collateral coronary flow has been developed. It was our purpose therefore first to examine the reliability of a number of possible criteria that suggested themselves to us and to draw conclusions regarding the effectiveness or ineffectiveness of a limited number of drugs in promoting a better collateral flow to ischemic areas.

In this report a number of possible expedients tried but found unserviceable will first be reported briefly and then a method that seems to have some merit will be detailed.

BLOOD FLOW FROM A PERIPHERAL CORONARY BRANCH AS A CRITERION

It is known to many experimenters that when a coronary ramus is ligated and the peripheral end is opened, blood oozes from the vessel.

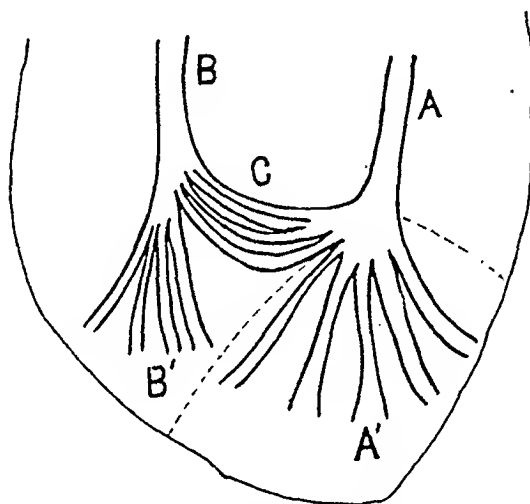


Fig. 1.—Schematic diagram illustrating relation of possible communications with any coronary branch. Discussion in text.

This blood must come from collateral sources. Many observers, including Anrep and Häusler,² and ourselves, had gained the impression that opening such a vessel tends to reduce the chance of fibrillation or of hypodynamic ventricular action. It proved easy for all of us to reach the conclusion, based on impression rather than experimental facts, that this is a collateral flow which is sufficient to maintain the normality of the area affected by coronary ligation. An examination of the facts necessitates the conclusion that such apparently beneficial effects either were not real or were fortuitous.

1. The blood issuing from a cut peripheral coronary vessel is red in color and cannot therefore have yielded oxygen for maintenance of contractions. This suggests that (referring to Fig. 1) blood flowing through collaterals *C* leaves the cut end of *A* and does not pass through intramural vessels *A'* at all.

2. The quantity of blood that flows from the peripheral end of the ramus descendens anterior, when measured in heparinized dogs by means of a horizontal micropipette, is exceedingly small—i.e., is of the order of 0.5 to 0.7 c.c. per minute. Flow rates that even approach those reported by Anrep and Häusler² from the peripheral end of the left circumflex ramus were never encountered from the peripheral end of the ramus descendens. It requires no calculations to conclude that such a small flow would be of insignificant value for a working left ventricle even if its oxygen were completely utilized.

3. Since Tennant and Wiggers³ had shown that occlusion of the ramus descendens anterior results within one minute in failure of contraction in the ischemic area, the expedient of simultaneously opening the peripheral end was tried, but no beneficial effect could be detected; failure of contraction occurred just as quickly. This offers unqualified proof of the inadequacy of the collateral flow, even when the vessel is opened.

The small magnitude of the flow and the difficulty of registering variations in the minute changes that occurred with alterations in blood pressure and heart rate made it apparent that such a criterion was too hazardous a one for determining whether these collateral channels can be opened sufficiently by drugs to make the collateral supply of functional value.

CHANGES IN PERIPHERAL CORONARY PRESSURE AS A CRITERION

During the early phases of our studies we saw no reason for questioning the view generally held that the pressure in a peripheral coronary vessel represents the pressure transmitted through various collaterals (Fig. 1, *C*) and that it constitutes the pressure head for flow through vessels *A'* when vessel *A* is occluded. It therefore appeared logical to suppose that, if the peripheral coronary pressure increases as a result of drug actions, a greater pressure head is created from collateral sources, regardless of whether this results from elevating pressure in the main branch *B* or from reducing the resistance in collaterals *C*. With vessel *A* occluded, the flow through intramural vessels would never be greater than such a rise of pressure indicated, although it might be less.

Experiments.—As a criterion of changes in collateral flow we first utilized comparative changes in mean carotid and peripheral coronary pressures recorded by properly damped mercurial manometers with carefully controlled hydrostatic levels. After opening the dog's chest, the ramus descendens anterior was ligated, and the peripheral end was cannulated and connected to a mercury manometer. Through a side tube the cannula was occasionally flushed with a small stream of oxygenated Locke's solution to which heparin had been added. This aided in prevention of fibrillation as well as coagulation. However, when fibrillation occurred, the heart could generally be revived by application of

about 1 amp. AC directly to the heart through padded moist electrodes. In many instances revival was accomplished four or six times without obvious harm to the circulation.

TABLE I

EXPERIMENT	AORTIC PRESSURE	CORONARY PRESSURE	APPROXIMATE PER CENT C OF A PRESSURE	HEART RATE
83	80- 86	16-18	20-21	182
84	102-104	26-27	25	167
87	109-114	27-29	25	217
88	75- 77	15	20	165
89	82- 87	21-23	26	190
90	81- 85	25	29-31	214
91	96-102	20-22	21-22	161
92	90- 96	26-28	29	167
93	102-104	23-24	23	174
94	83- 89	22-23	26	131
95	103-112	19-20	18-18.5	169
96	81- 84	22	26-27	153
97	82- 84	27-29	33-35	144
100	96- 97	11-12	11.5-12	179
104	82- 98	17-21	20-21	147
105	108-109	17-18	16-16.5	197
107	60- 80	16-17	21-27	183
111	110-116	30-32	27-28	170

The results of eighteen experiments incorporated in Table I show that, when mean aortic pressure ranged from 68 to 116 mm. Hg, the extreme ranges of peripheral coronary pressure were between 11 and 32 mm. Hg or, otherwise expressed, equaled 11 to 35 per cent of aortic pressure. In twelve instances it equaled from one-fifth to one-fourth the systemic arterial pressure—ratios that may be regarded as roughly approximating that of average dogs under normal conditions. If this really represents collateral pressure, it should be quite adequate to sustain the area deprived of its normal supply.

Since many drugs acting upon coronary vessels produce changes in blood pressure and heart rate, the extent to which these influences alter peripheral coronary pressure needed to be studied. A few of the results are incorporated in Table II. The relationship to systemic pressure, when the latter was elevated either by compressing the aorta or through stimulation of afferent nerves, was studied in fifteen dogs. Consistently peripheral coronary pressure rose and fell with aortic pressure although the ratio of aortic to peripheral coronary pressure sometimes increased with a rise in pressure (cf. Experiments 78, 88, 92, 93, 107, Table II). No differences were noted between experiments in which the increase in aortic resistance was produced by mechanical aortic compression and those in which it was caused by general reflex vasoconstriction. Heart rate changes were produced by stimulating a peripheral end of the right vagus nerve and by rhythmic excitation of the right auricle, the resulting changes in blood pressure being compensated by graded compression of the thoracic aorta. Table II also shows results of a few such experi-

TABLE II

ABRIDGED DATA SHOWING RELATIONS OF MEAN AORTIC AND MEAN PERIPHERAL CORONARY PRESSURES WHEN AORTIC PRESSURE AND HEART RATE WERE VARIED SEPARATELY

EXPERIMENT	AORTIC PRESSURE	PERIPHERAL CORONARY PRESSURE	RATIO	HEART RATE PER MINUTE	REMARKS
78	76*	18	4.2	133	Control
	100*	25	4.0	139	Aortic compression
	184*	35	5.3	124	Aortic compression
	80*	18	4.4	113	Compression released
	140*	27	5.2	114*	Central vagus stimulation
	77*	24	3.2	136	Control after
	146*	35	4.2	138*	Control after
	161*	41	3.9	161	Control after
87	113	20	5.7	60*	Vagus stimulation
	108	22	4.9	115*	After
	115	29	4.0	217*	Artificial stimulation auricle
	132	25	5.3	109†	Control
	132	32	4.1	179†	Artificial stimulation auricle
	125	25	5.0	111*	Control
	127	30	4.2	194*	Artificial stimulation auricle
88	100	29	3.5	161*	Aorta partially compressed
	87*	28	3.1	150	Aorta released
	114*	30	3.7	150	Aorta partially compressed
	88*	28	3.1	150	Aorta released
	100	24	4.2	125*	Peripheral vagus stimulation
	100	36	2.8	185*	After
89	92	32	2.9	185*	Control
	92	26	3.5	106*	Peripheral vagus stimulation
	96	25	3.8	96*	Peripheral vagus stimulation
	96	36	2.7	187*	After
92	129*	40	3.2	167	
	107*	34	3.1	167	
	38*	16	2.4	155	Spontaneous circulatory failure
	100*	26	3.8	150*	Aortic compression
	100	20	5.0	84*	Peripheral vagus stimulation
93	66*	22	3.0	103	Pilocarpine slowing
	102*	27	3.8	106*	Plus aortic compression
	100†	28	3.6	156*	Natural recovery
	102	27	3.8	114*	Peripheral vagus stimulation
	102	30	3.4	181*	After
	54†	23	2.3	142	Circulatory failure
107	60*	16	3.8	177	Control
	80	17	4.7	183	Venous infusion
	112*	27	4.2	187	

*Denotes changes to which attention should be specifically directed.

†Denotes two sets of figures to be especially compared, independent of those marked by the asterisk.

ments. They seem to show that, whenever the heart beats change from an initially high to lower rate, the peripheral coronary pressure tends to lessen (cf. Experiments 88, 89, 92, Table II); and vice versa, when the rate increases, it tends to rise (cf. Experiments 78, 87, 93). Since aortic pressure in all of these instances remains practically unchanged, the ratio of aortic to peripheral coronary pressure decreases as the heart accelerates.

With these effects of changes in systemic blood pressure and heart rate as a guide, the consequences of a number of drugs up to and often exceeding therapeutic doses were studied. In reviewing a large collection of records there was found no single instance in which (a) inhalation of amyl nitrite, 50 per cent oxygen, 6 to 10 per cent carbon dioxide or (b) intravenous injections of sodium nitrite, nitroglycerin, theobromine, aminophylline, alcohol, pitressin, epinephrine, or synephrin produced any change that could not be attributed to changes in arterial pressures. When systemic pressure did not change or when it was compensated by aortic compression or decompression, peripheral coronary pressures remained unaffected.

A strict interpretation of such results in accordance with the generally accepted view that peripheral coronary pressure represents transmitted collateral pressure would lead to the conclusion that no evidence exists that collateral flow is affected by drugs in any way other than through changes in general blood pressure, i.e., drugs causing a fall of arterial pressure reduce collateral flow; those increasing it augment the flow.

Another interpretation proved more probable, viz., that such peripheral coronary pressures *are due not to transmitted pressure* but to compressing action of the ventricle upon intramural vessels and therefore do not serve as an index of collateral coronary flow. These conclusions were arrived at as a result of complicated dynamic studies the details of which are published elsewhere. In brief, Gregg, Green, and Wiggers⁴ meanwhile made the discovery that the initial rise of peripheral coronary pressure occurs previous to elevation of the aortic pressure pulse and that at the very beginning of diastole it falls rapidly to a low level, not gradually as arterial pulses do. These temporal differences alone preclude the assumption that variations of pressure in the peripheral coronary vessel are occasioned by transmission of arterial pressure waves. Furthermore, optical curves showed that the rise in peripheral coronary pressure that follows elevation of aortic pressure due to aortic compression is due chiefly to greater rises of individual pressure pulses during the period of isometric contraction. This indicates that the concordant rise of mean peripheral coronary and aortic pressures is fortuitous and that changes in peripheral coronary pressure are related primarily to increase in intramural tension and only to higher aortic pressure so far as this augments the contractile stress of the left ventricle. With such revision of our concepts regarding the significance of peripheral coronary pressure, its use as a criterion of coronary collateral flow had to be abandoned.

CHANGES IN INFLOW RATE AS A CRITERION

The idea occurred to us that changes in the coronary inflow rate of a perfused branch of the intact heart can be used not only as a criterion of flow changes through its distributing intramural branches but of changes in collateral supply as well. The principle can be easily un-

derstood by reference to Fig. 1. If branch *A* be ligated and the peripheral end be perfused with Locke's solution at a pressure *equal to the aortic pressure*, then the pressure in vessels *A* and *B* will be essentially equal and opposite; no flow occurs through channels *C*; and the perfusion fluid must drain through vessels in area *A'*. If the caliber of the latter changes or their average muscular compression alters as a result of drugs added to the perfusion fluid, the rate of flow into vessel *A* should change.

If, on the contrary, vessel *A* be perfused at pressures considerably above the aortic pressure, the runoff from vessel *A* could occur either through *A'* or *C*. If now pressure in the perfused branch be reduced to a low level, e.g., 20 to 30 mm. Hg, *while a drug is injected into the general circulation*, an opportunity should be given for it to pass from vessel *B* by collateral channels *C* into the terminals of *A*. If drugs injected into the general circulation reach and act either upon vessels *C* or *A'*, the inflow rate into vessel *A* at pressures considerably above aortic should alter—increasing if the resistance were reduced and decreasing if it had been decreased.

During the time that these experiments were actually carried out, we were convinced that changes in vascular resistance induced by drugs could probably be referred solely to vascular changes because the ischemic region studied was not contracting. The assumption made that changes of extravascular tension could not be concerned proved untenable, however, as our studies continued. Gregg, Green, and Wiggers⁴ found that peripheral coronary resistance is increased just about as much when the area is stretched by the force of intraventricular tension as when it develops tension through its own contraction. Continuing these studies, we found that the degree of systolic stretch and the mechanical increase in peripheral coronary resistance ran approximately parallel to changes in intraventricular tension. Thus all increased during each systole when arterial pressures were elevated as a result of aortic compression or reflex general vasoconstriction, and all decreased during each systole when arterial pressure declined as a result of reflex general dilatation or hemorrhage. Similar complicating effects would doubtless occur during the use of drugs with pressor or depressor effects on general blood pressure. Furthermore, even when aortic pressures were but slightly affected by drugs such as those of the methyl purine group, the possibility that heart rate changes might modify resistance could not be excluded.

These complications were unfortunate in that the method appears unsuitable as a criterion for determining alterations of collateral flow to an ischemic area, following use of drugs. They were fortunate because it does offer a criterion of the changes in resistance to flow which are the resultant of vasomotor and extravascular effects, which ines-

capably operate together when a drug is administered. Since the conditions resemble those following coronary occlusion in man, the actions discovered should be of considerable practical importance.

Experimental Application of the Principle.—Several procedures could be used to record the rate of flow into a peripheral coronary vessel. We devised a method which measured the time required for 1 or 2 c.c. of Locke's solution to flow under pressures declining between fixed levels, near but above mean aortic pressure. A schematic diagram of the apparatus is shown in Fig. 2. Oxygenated Locke's solution at body temperature from a "constant pressure" bottle was continuously perfused through the cannulated ramus descendens, *C*, by use of a shunt, *E*.

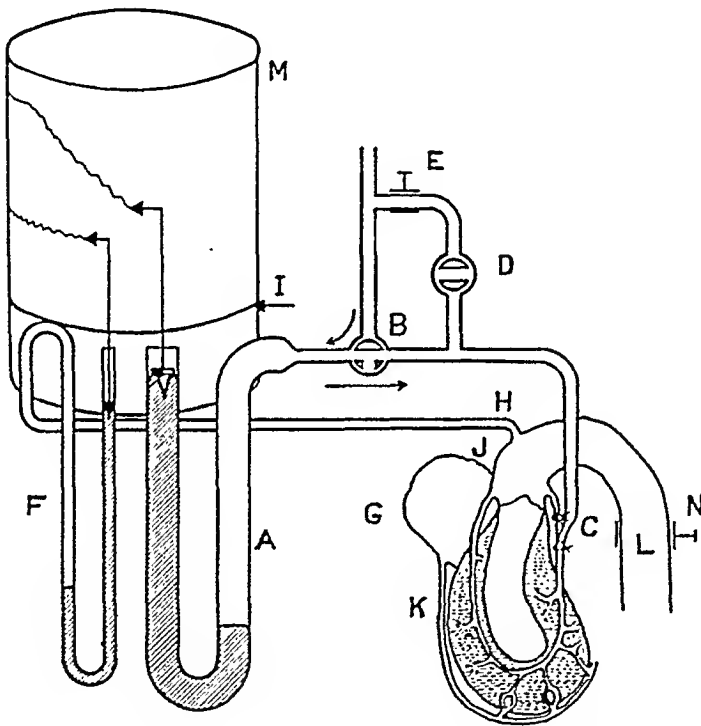


Fig. 2.—Scheme of apparatus for testing coronary flow after possible action of drugs on collateral flow. Discussion in text.

While this flow continued, Locke's solution from the same source was introduced by a three-way stopcock, *B*, communicating with the mercury manometer, *A*, until the mercury and its float had risen to 180 or 200 mm. Hg. The limbs of this manometer were of such size that every centimeter rise or fall of the stylus writing upon the drum represented a volume change of 1 c.c. in the manometer and, of course, a 20 mm. Hg pressure change.

A flow test was carried out by closing stopcock, *D*, and turning stopcock, *B*, simultaneously so that Locke's solution from manometer, *A*, flowed at gradually declining pressure through cannula, *C*, while the kymograph drum, *M*, moved at an even speed. Time was recorded in

0.2 sec. The carotid or subclavian mean pressure was simultaneously recorded by another mercury manometer, *F*. Meticulous care was exercised to have the zero levels of the two manometers exactly the same.

The temperature of the perfusion fluid was maintained constant by submerging the entire manometer, *A*, and all connecting tubes to within a short distance of the cannula in a water-bath, thermostatically controlled.

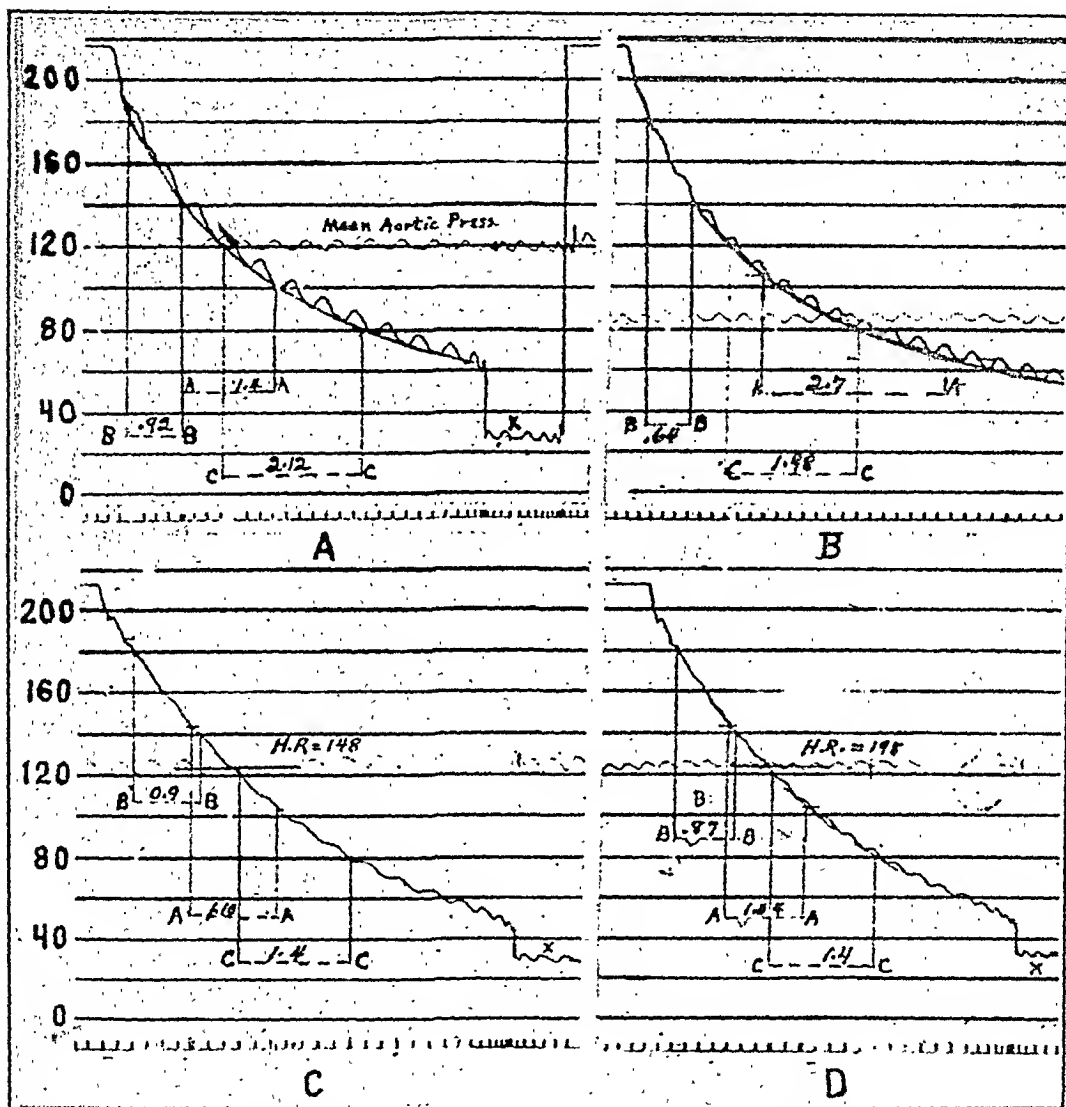


Fig. 3.—Curves showing rate of coronary inflow under declining pressures in relation to mean aortic pressure.

A, control; *B*, after sodium nitrite; *C*, control; *D*, after theamin. Ordinates, mm. Hg. Analysis in text.

Each experiment consisted in determining the control inflow rates three or four times under declining pressures. After the last of these control tests, the pressure was allowed to come into equilibrium with peripheral coronary pressure by keeping stopcock, *D*, closed, thus reproducing conditions that exist during coronary occlusion. A drug was then administered, care being taken to give it at such a rate that arterial mean pressure was altered as little as possible. After one to

three minutes—or sooner when definite evidence of its action upon the circulation was otherwise evident—a number of flow determinations were repeated in succession.

Method of Analyzing Reactions of a Typical Experiment.—Curves *A* and *B* of Fig. 3 serve as specimen records of results before and after administration of 3 c.c. of 10 per cent sodium nitrite solution. The curve of Fig. 3, *A*—one of three controls—shows in addition to mean aortic pressure, the parabolic decrease in inflow rate as the perfusion pressure declines from 200+ mm. to about 60 mm. Since mean blood pressure was about 120 mm. Hg, the time required for 2 c.c. to flow between a pressure drop from 140 > 100 mm. Hg was first determined at distance *A - A*. This equaled 1.40 sec. and denotes the rate of runoff at existing mean pressure. To be quite certain that some runoff from any existing collaterals (Fig. 1, *C*) would be included, the rate of inflow was also determined at considerably higher pressures, viz., from 180 > 140 mm. Hg (*B - B* = 0.92 sec.). To establish still a lower range in which runoff from any existing collaterals would be less likely to occur, the time required for flow between 120 > 80 mm. Hg was determined as *C - C*, which equaled 2.12 seconds. The pressure was then allowed to seek its level at 27 mm. Hg as shown at *X*. During this time sodium nitrite was administered via a femoral vein. It caused a typical fall in mean pressure. As soon as the maximum drop had been attained the record of Fig. 3, *B* was taken. Since the mean pressure had fallen to 84 mm. Hg, the flow rate at 84 ± 20 mm. was again determined as distance *A - A*. As expected, this increased the runoff time for 2 c.c. to 2.7 sec. Calculated on a flow per minute basis, the flow approximately decreased from 85 to 44 c.c. per minute. Since collateral pressure also decreased, the only effect on collateral flow could be a decrease regardless of whether the drug reached and acted upon the vessels. Such observations effectively demonstrate the fallacy of the idea that coronary dilation accompanied by lower arterial pressure can improve blood flow. To determine whether the drug had any effect on peripheral coronary resistance, the rate of flow during the pressure drops from 180 > 140 mm. Hg and from 120 > 80 mm. Hg was determined as before. They are indicated at *B - B* and *C - C*, respectively. Measurement showed that the duration of *B - B* was 0.62 sec. and of *C - C*, 1.98 sec. This amounted to an increase in the runoff *B - B* from 130 c.c. per minute to 187 c.c. per minute, and in the case of *C - C* from 56 c.c. per minute to 60 c.c. per minute. This one of our most favorable reactions denoted a slight decrease in peripheral resistance to runoff at high equivalent pressures.

The action of other drugs was analyzed in a similar way, and the results as regards comparative runoffs at high pressures (*B - B*) may be briefly described.

Effects of Drugs Causing No or Insignificant Changes in Mean Arterial Pressures.—In two experiments 200 mg. of theobromine sodium acetate increased the flow from 91 to 105 e.c. per minute in one and decreased it from 105 to 94.3 e.c. per minute in another.

In three experiments from 15 to 60 mg. of monoethanolamine-theophylline (theamin, Lilly) increased the minute flow insignificantly, as follows: $83 < 85$ e.c. per minute, $85 < 90$ e.c. per minute; $67 < 74$ e.c. per minute. Figure 3 C and D illustrates the very insignificant increase in flow rates of one such test following use of 85 mg. of theamin.

In one experiment 15 mg. theophylline sodium acetate decreased the flow slightly from 73 to 70.6 e.c. per minute.

Ethylenediamine-theophylline (aminophyllin, Searle) was tested in two experiments, but, as the controls failed to check, no positive conclusions may be drawn.

Intravenous infusion of small and large volumes of 10 per cent alcohol produced no discoverable change in three tests. The conclusion cannot be escaped that neither theophylline compounds nor alcohol produces a favorable combination of dynamic effects leading to significant improvement of collateral flow.

Effects of Drugs Causing a Fall in Mean Arterial Pressure.—Sodium nitrite was administered in eight experiments in doses ranging from 20 to 240 mg. The changes in B-B flow were either nil, or a slight augmentation resulted. The latter may be illustrated by the following values: $54.3 < 60.6$ e.c. per minute; $151 < 171$ e.c. per minute; $166 < 181$ e.c. per minute; $187 < 193$ e.c. per minute. Whether these changes can be attributed to vasodilation or are due to decreased extravascular resistance caused by lesser tension developed by the ventricle remains undetermined. In any event such slight reduction in resistance could scarcely be important in producing a better blood supply under conditions in the body, for as arterial pressures fall, the pressure head in the supplying artery (Fig. 1 B) would also decrease. Calculations of flow rates at perfusion pressures ± 20 mm. of aortic pressure (A-A flows) always showed a marked reduction. The conclusion was drawn that there is no evidence that the collateral supply is increased by use of the nitrite group. The slight reduction in resistance to flow at equivalent testing pressures is probably due to decreased extraarterial compression of coronary vessels following lowered arterial pressure and decreased stretch of the ischemic area. This slightly beneficial effect is more than offset, however, by the lowering of pressure in other branches from which collateral flow could be derived.

Effect of Drugs Causing a Rise in Mean Pressure.—In six experiments 5 to 10 per cent carbon dioxide was administered with oxygen, and the mean pressure rose slightly as a result. The flow effects were negligible. In some cases they consisted in a slight increase; in others a slight de-

crease as is evident from the following effects on $B - B$ flow: $104 < 111$; $161 \rightarrow 161$; $154 < 167$; $240 > 200$; $200 > 181$; $142 < 181$ c.e. per minute.

In three experiments the animal was partially asphyxiated by discontinuing the artificial respiration. A consistent slight decrease in minute flow occurred each time.

Epinephrine in concentrations of 1:400,000 to 1:50,000 was administered very slowly. In nine tests only a slight reduction in flow was

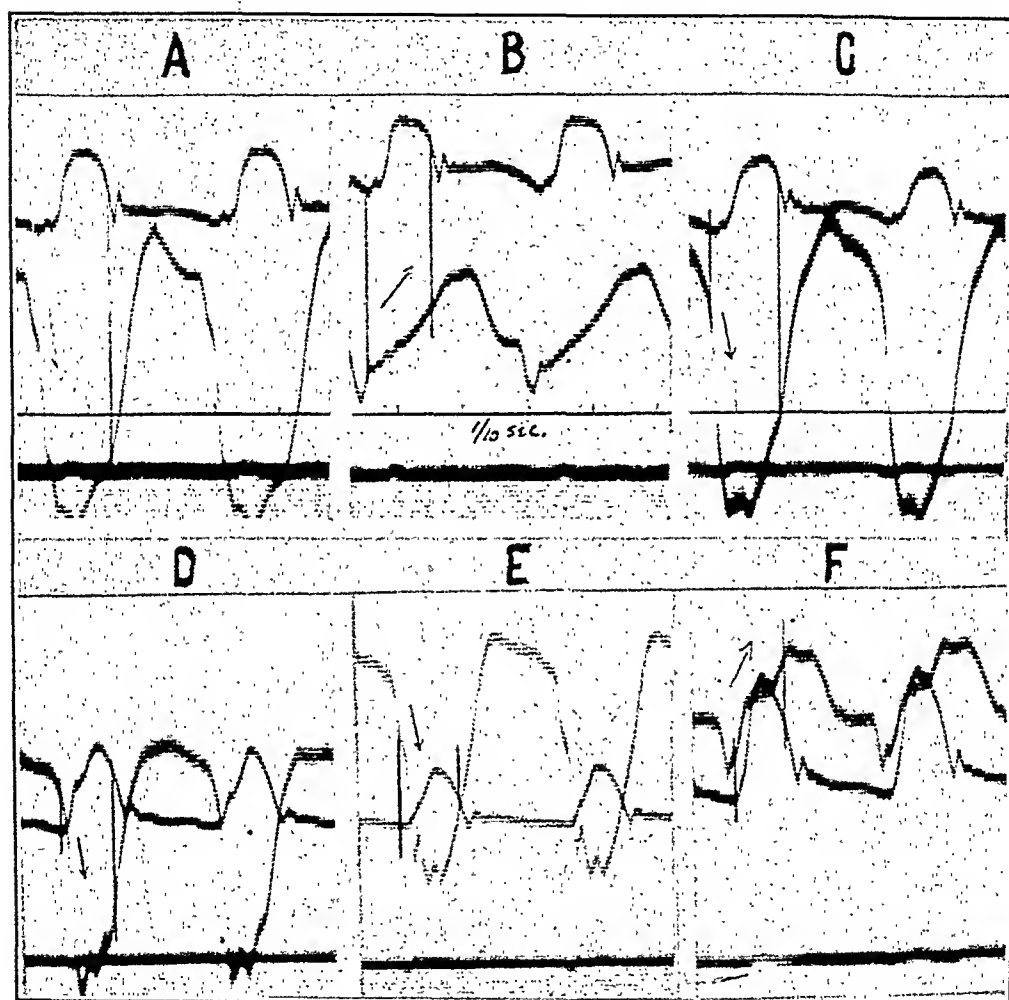


Fig. 4.—Six segments of records showing behavior of a ventricular area studied myographically (lower curve) and aortic pressure (upper curve). Arrows pointing downward denote expansion of area during systole, those pointing upward denote contraction. Discussion in text.

found as indicated by the following data: $42.5 > 38.5$ c.e. per minute; $78.5 > 75.5$ c.e. per minute; $70 < 79 > 59$ c.e. per minute; $101 > 87$ c.e. per minute; $92 > 83$ c.e. per minute; $109 > 92$ c.e. per minute; $157.5 \rightarrow 157.5$ c.e. per minute.

In eight experiments synephrin tartrate also consistently produced a decrease in volume flow, e.g., $76.0 > 65.5$ c.e. per minute; $83.0 > 70$ c.e. per minute; $76.5 > 57$ c.e. per minute; $103.5 > 101.5$ c.e. per minute;

65 → 65 c.c. per minute; 163.5 > 100 c.c. per minute; 130 > 100 c.c. per minute; 75 > 60.5 c.c. per minute.

Such a sampling of drugs having a dilating action on coronary vessels under uncomplicated conditions does not encourage the belief that the collateral blood supply to an ischemic area can be significantly improved by use of any drug.

EFFECT OF DRUGS ON MYOGRAPHIC CHANGES IN THE ISCHEMIC AREA

The myographic demonstration by Tennant and Wiggers² that the muscular area supplied by the ramus descendens ceases to contract and vigorously expands within about one minute after occlusion of its supplying branch indicates that the collateral supply which normally exists is not sufficient to maintain contraction of that region of the ventricle. If any drugs act to increase the collateral supply significantly, their injec-

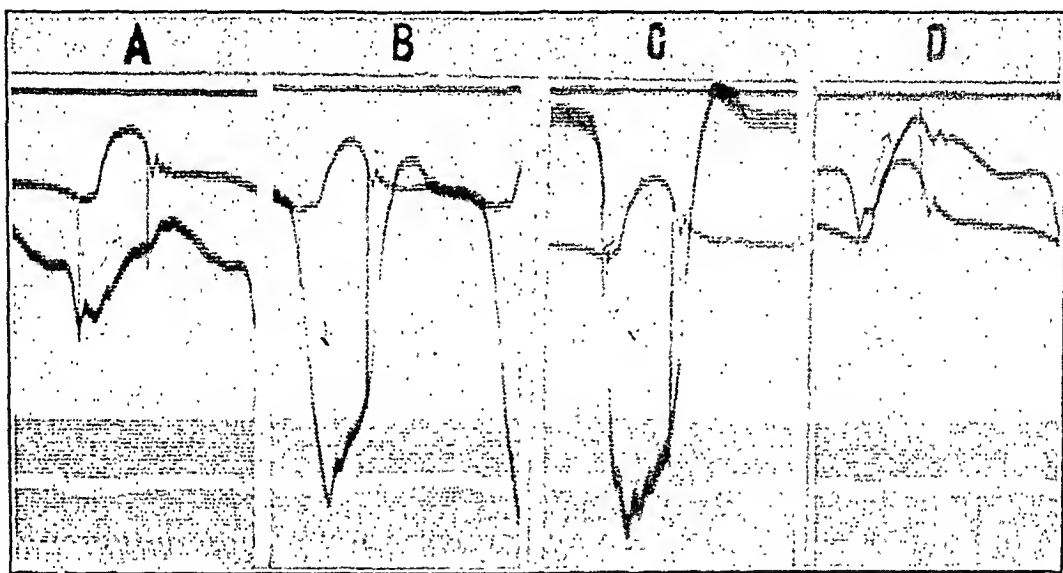


Fig. 5.—Curves similar to those in Fig. 4. The electrographic record should be ignored. Time, 0.02 sec. Discussion in text.

tion, from 1 to 2 minutes after occlusion, should cause some amelioration of the systolic muscular expansion and perhaps some sign of contractile recovery, such as promptly follows unclamping of the main artery.

Experiments.—A myograph connected to a segment capsule was applied as described by Tennant and Wiggers. Aortic pressure was recorded simultaneously. Two series of sample curves indicating the character of responses are shown in Figs. 4 and 5. Figure 4 *A* illustrates the expansion of the ischemic area induced 2 minutes after a preliminary trial clamping of the ramus descendens anterior. Segment *B* illustrates the degree of recovery 1 minute 20 seconds after unclamping the vessel. Segment *C* again shows that the expansion induced by a second clamping is still present 2 minutes 28 seconds after 14 mg. ethylenediamine-theophylline (aminophyllin ampules, Searle) had been injected into a femoral vein. This was followed by a decline of aortic pressure as illus-

trated in segment *D* taken 3 minutes later. No suggestion of contractile recovery exists; the degree of systolic distention is merely less, due to the less vigorous action of the left ventricle. At this time an additional 10 mg. of the drug was given, and 2 minutes later the record of segment *E* obtained in which the myogram was shifted for convenience by adjustment of the Frank capsule only. No evidence of a restoration of contraction exists. Three minutes later the ramus descendens was released, and 1 minute 15 seconds later the record of segment *F* was recorded. Though recovery is not quite complete, evidence of good contraction occurs upon restoration of the normal blood supply.

Similar results were obtained from eight similar trials of various theophylline preparations, all indicating that the collateral circulation is certainly not improved sufficiently by any of these preparations to restore contractions.

Figure 5 *A* shows a normal shortening in the myographic curve and *B* illustrates the pronounced systolic stretching exactly 1 minute after occlusion of the ramus descendens anterior. Segment *C* shows the continued systolic stretching 2 minutes after administration of 30 mg. adenylic acid. As no reversal occurred for 6 minutes, the vessel was unclamped, and curves of segment *D* were recorded 1 minute later. Since improved blood supply promptly restores contraction, but adenylic acid in five trials on different animals showed no sign of such recovery, its potency to augment collateral blood supply must be negligible.

In a similar manner we tested the action of amyl nitrite, sodium nitrite, ouabain, rebreathing pure oxygen, and the effects of hypercapnia. In no single instance was any suggestion of contractile recovery noted.

The experiments were also varied by administering the various drugs just before coronary occlusion (from 30 sec. to 2 min.). It was found, however, that contractions ceased just as promptly after coronary occlusion as without medication.

SUMMARY AND CONCLUSIONS

Valid experimental evidence as to whether a drug can improve collateral blood flow to an ischemic area is difficult to obtain. Observation of color changes or comparison of size of infarcts without and with use of a drug are subject to too many contingencies to have a certain value. Observations as to the effects of drugs upon coronary inflow and outflow do not test the response of collateral vessels and ignore the hemodynamic alterations resulting from occlusion of the main branch.

We therefore studied the reliability of four other possible criteria of changes in collateral flow, viz., (1) changes in rate of blood flow from a peripheral coronary ramus; (2) alterations in mean peripheral coronary pressure; (3) changes in inflow rate at high perfusion pressures before and after use of drugs—the latter being administered during a period

when the area was not perfused; and (4) the ability of drugs given by inhalation or intravenously to prevent contractile failure after ligating a ramus or of restoring such contractions in an ischemic area.

Evidence and reasons are presented why the first and second of the methods cannot be used as criteria. The third method also proved to be no criterion of changes in collateral flow alone but is useful because the flow changes are a *resultant* of vascular and extravascular factors which modify resistance to flow. The following results were obtained:

1. Drugs of the theobromine and theophylline group have a very insignificant effect on flow through an ischemic region.

2. The nitrite group causes a slight decrease in coronary resistance within the ischemic area, but it appears more probable that this is due to attendant reductions of intraventricular tension rather than to effects of drugs reaching the vessels of an ischemic area. At any event this slightly beneficial action is more than offset by the fact that the driving pressure in larger collateral vessels in the left ventricle is reduced.

3. Pressor drugs such as epinephrine and synephrin consistently increased resistance to inflow in the ischemic area. If these drugs exert a dilating vascular action, it is overpowered by greater extravascular pressures in intact hearts.

The fourth method offers conclusive evidence as to whether collateral blood supply increases to a degree to be of functional use. This is ultimately the important question. Our results show that the abolition of contraction about one minute after occlusion of the ramus descendens anterior is not modified in the least by inhalation of oxygen, carbon dioxide, amyl nitrite, or by therapeutic intravenous doses of various theophylline preparations, nitrites, adenylic acid or epinephrine.

A sufficient sampling of possible useful drugs by these methods necessitates, we regret, the conclusion that an increase in collateral circulation sufficient to be of functional use cannot be attained by use of vasodilating drugs after complete coronary occlusion.

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THE PARADOX OF CHIARI'S NETWORK

REVIEW AND REPORT OF A CASE OF CHIARI'S NETWORK ENSNARING A LARGE EMBOLUS*

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IT IS hoped that the title of this paper will stimulate interest in a cardiac anomaly which is not exactly rare but concerning which there is little general knowledge. In 1929, I published an article entitled "Variations and Anomalies of the Venous Valves of the Right Atrium of the Human Heart." This article was a review of the knowledge of the subject and report of an original study of the variations and anomalies of these valves in 120 routinely collected hearts, all of which would be considered developmentally normal. A eustachian valve, or valve of the inferior vena cava, was found to be present in some form in all but seventeen of these hearts. A thebesian valve, or valve of the coronary sinus, was found to be present in some form in all but thirteen of them. These figures indicate well the high incidence of such venous valves, which may be considered therefore normal parts of the adult human heart, although they vary greatly in structure and apparently serve no useful purpose in the economy of the extrauterine life of the heart.

EMBRYOLOGY OF THE VENOUS VALVES

Both the eustachian valve and the thebesian valve are remnants of the right valve of the sinus venosus. In the embryonic development of the heart, according to the works of His, Born, and Röse, the single atrial cavity is divided into its two definitive chambers in the following manner: The septum primum arises from the middorsal wall of the atrium and eventually fuses with the endocardial cushions at the junction of the atrial and ventricular cavities. Perforation of the septum primum occurs to form the foramen ovale. This is subsequently closed by the fusion of the left valve of the sinus venosus and the septum secundum which appears in close proximity to the septum primum as an outgrowth from the ventral and caudal wall of the right atrium (Fig. 1).

The right horn of the sinus venosus lags somewhat and is taken up in the wall of the right atrium, which causes the opening into the right atrium of the superior and inferior venae cavae. The right valve of the sinus venosus at one time nearly divides the right atrium into two chambers; but later it becomes progressively lower, its cephalic portion remaining as the crista terminalis, its caudal portion being divided to form the valve of the inferior vena cava (eustachian valve) and the

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valve of the coronary sinus (thebesian valve). As the left horn of the sinus venosus is migrating across the posterior wall of the atrium during the stage of absorption of the remainder of the sinus, it projects into the lumen of the atrium as the inferior sinus septum and divides the caudal portion of the right sinus valve into these two definitive valves. The opening of the left horn of the sinus venosus is the left duct of Cuvier, which is thus pulled over to a place beneath the orifice of the inferior vena cava and persists in part as the coronary sinus. The septum spurium is a vertical ridge formed by a fusion of the right and the left valves of the sinus venosus on the dorsal and cephalic wall of the right atrium, and this is also taken up into the wall of the atrium as it expands. It remains partly, however, to form the uppermost portion of the crista terminalis, where it separates sharply the orifice of the superior vena cava from the atrial appendage.

The eustachian valve serves to direct the blood in embryonic life from the inferior vena cava into the left atrium through the foramen ovale.

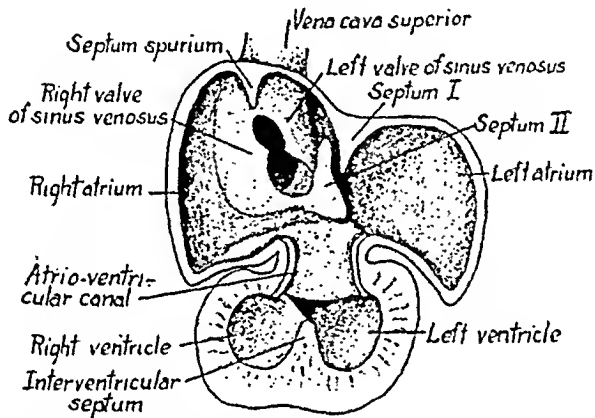


Fig. 1.—Inner view of dorsal wall of heart of 10 mm. human embryo. Drawn from a Ziegler model of one of His's embryos (after Jordan, H. E., and Kindred, J. E.; Textbook of Embryology, New York, 1926, D. Appleton and Co.).

The thebesian valve possibly serves to prevent regurgitation of blood into the coronary sinus during auricular systole. This supposition, however, seems unlikely, since the thebesian valve is usually incompetent, that is, it is not sufficiently extensive to close the orifice of the coronary sinus, or if so, is usually fenestrated.

DESCRIPTION OF THE ADULT VALVES

The eustachian valve is usually a muscular and membranous fold in the right atrium extending posteriorly from below the fossa ovalis and then upward just anterior to the orifice of the inferior vena cava, in the upper portion of which it is lost. Its free margin is concave and directed upward and forward, its adherent border convex and directed downward and backward. One of its surfaces is turned laterally toward the atrium, the other medially toward the vessel. The lower portion is a transverse muscular ridge (the sinus septum) continuous with the limbus

fossa ovalis; the upper portion is usually membranous. Often the membranous part of the valve contains thin strands of ordinary cardiac muscle, especially in its attached portion. Often, also, it has fenestrae, and sometimes thin strands of endocardium are attached at points along its edge or form a little network there. The valve is usually not more than a centimeter wide in the adult. In some cases the eustachian valve is very inconspicuous or may be entirely lacking. In others it may be very broad and project far into the right atrium. Sometimes it is thin and flabby, sometimes fibrous and taut.

The thebesian valve is directly below the lower portion of the eustachian valve in the space between this and the edge of the atrioventricular foramen at the junction point of the lower portion of the interatrial septum and the posterior wall of the atrium in close association with the

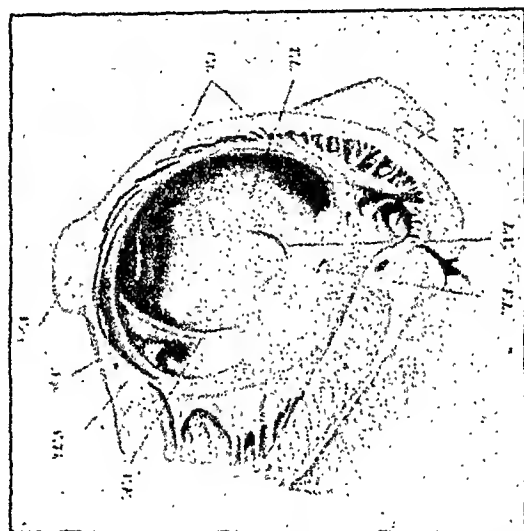


FIG. 2.—Right atrium with the lateral wall removed to show the relationship of the orifices of the atrium and the usual forms of the eustachian and thebesian valves; V.E., eustachian valve; V.Th., thebesian valve; A.P., auricula posterior; V.I., inferior vena cava; C.T., crista terminalis; T.L., tuberculum loweri; V.S., superior vena cava; L.V., limbus Vieussentii; F.L., foramen Lannelongue (after Tandler, Jullier, in Bardeleben: *Handbuch der Anatomie des Herzens*, Jena, 1913, Gustav Fischer).

mouth of the coronary sinus, to which it is usually placed laterally. It is frequently semihmar or crescentic, with its anterior free edge concave and its posterior attached edge convex. It is often fenestrated or made up of a network of threads. In fact, its size and form are extremely variable. It may be absent or represented merely by a thin, narrow ridge on the posterior edge of the mouth of the coronary sinus, or it may be present as a large membrane completely covering the sinus orifice. It may even be anterior to the orifice, placed obliquely, transversely or vertically across it. Usually it is very thin and translucent. Sometimes there is a definite connection between it and the eustachian valve. The orifice of the coronary sinus with its valve often lies in a sacular depression between the lower portion of the eustachian valve

and the atrioventricular rim; this is the appendix auricularis posterior of His or the subeustachian sinus of Keith. Figure 2 shows the most frequent form of the valves and their relationships in the atrial cavity.

ANOMALIES OF THE VALVES OF THE RIGHT ATRIUM

Anomalies of these valves are dependent on the degree of completeness of regression of the right and left valves of the sinus venosus, the septum spurium, and the sinus septum. Hearts with defective development of the interatrial septum may contain all grades of persistency of these four structures, but the completely developed heart presents relatively few types of anomalies of the valves. In the adult heart rudiments of the right venous valve are found at the sharp anterior rim of the orifice of the inferior vena cava, extending upward to the upper portion of the crista terminalis and downward across the orifice of the coronary sinus toward the tricuspid orifice. Remnants of the left venous valve are located on the interatrial septum in the posterior region of the annulus fossae ovalis and the intervenous tubercle (*tuberculum loweri*), which is merely an eminence superior to the fossa ovalis between the orifices of the venae cavae. Residual structures of the septum spurium would be found anterior to the mouth of the superior vena cava near the interatrial septum. Remnants of the sinus septum are seen normally in the muscular ridge which extends from the lower end of the limbus fossae ovalis to the inferior part of the rim of the orifice of the inferior vena cava and becomes a part of the normal eustachian valve. If the inferior sinus septum merely fuses with the right venous valve and does not divide it, the eustachian and thebesian valves are formed as a continuous fold with an attachment to the wall of the atrium in the region of the inferior sinus septum. Should the inferior sinus septum fail entirely, the two valves will be a simple membrane or reticulum unattached except perhaps posteriorly to the wall of the atrium.

CHIARI'S NETWORK

It is not my purpose in this paper to mention every article ever written upon the variations and anomalies of the venous valves of the right atrium. Since 1865, when Lindes described the malformed heart of a newborn infant with persistence of the right and left venous valves, there have been twenty-nine publications on this subject, an average of one article every two and one-half years. Since my review in 1929 of all previous articles, there have been three additional reports (Hueper and Berghoff, Alvarez and Herrmann, and Helwig). Particular interest has been taken in an anomaly of these valves known as Chiari's network. In 1897 H. Chiari reported eleven cases of an anomaly consisting of a network of fine or coarse fibers in the right atrium, its attachments extending from the interatrial septum or upper portion of the crista terminalis to the thebesian and eustachian valves or to the region of the

orifices of the coronary sinus and inferior vena cava. In one case the network was responsible for the death of the patient, a young man of twenty-four. There was extensive pulmonary embolism, the source of which was apparently a thrombus which had formed in the confluence of the fibers of the network. In eight others the network was incidental, although three of the patients died of heart disease.* None of Chiari's cases showed any other relevant congenital anomalies.

Since Chiari's description of the network, 25 instances of a similar formation have been reported (A. Weber, 1; LeComnt, 1; Looser, 1; Ebbinghaus, 1; Thilo, 2; Haas, 1; F. P. Weber, 2; Jordan, 2; Yater, 4; Hueper and Berghoff, 2; Alvarez and Herrmann, 1; Helwig, 7). In addition to these Mönckeberg states that in Düsseldorf in two years he observed 6 typical examples of Chiari's network in persons aged from twenty-four to fifty-nine years. He did not, however, describe these cases. This anomaly occurs probably in between 2 and 3 per cent of hearts.

The designation, Chiari's network, should be confined, probably, to those reticula in connection with the eustachian and thebesian valves which have threads attached in the upper region of the right atrium, near the crista terminalis, or to the interatrial septum in the region of the tuberculum loweri.

This formation does not usually cause a murmur, although Alvarez and Herrmann attributed to such a network a peculiar, low pitched "thonging" hum heard along the right sternal border from the third rib downward, mainly in diastole. However, this was accompanied by the diastolic murmur of aortic regurgitation due to syphilitic aortitis with involvement of the aortic valve.

Method of Opening Heart to Preserve Network.—In a heart opened in the usual routine manner, the eustachian valve is cut almost directly through its middle by the scissors as it passes between the orifices of the two venae cavae. If a network is present, the cut fibers collapse against the wall of the atrium and are not usually observed upon inspection of the atrial cavity. To preserve the network one should open the right atrium by an incision into its wall just above and parallel to the atrioventricular junction without cutting the rim of the orifice of the inferior vena cava. The incision may be extended to the tip of the atrial appendage. It is well to look through the open end of the inferior vena cava before making the incision in order to determine whether a network exists.

THE PARADOX OF CHIARI'S NETWORK

The reason for this designation is that, although probably not often of clinical importance, the network in some cases may be responsible for death from pulmonary embolism, while in others it may prevent death

*In two cases the cause of death was not given.

from this cause. In a certain number of cases there is noted an increased facility for the formation of thrombi on the fibrous threads of the network. In the literature nine instances are recorded in which such thrombi were present, and in one (Chiari's Case 1) there was no doubt that the thrombus was the cause of fatal pulmonary embolism. In one of my cases also the patient died of pulmonary embolism, but there was, in addition, extensive thrombosis of several large veins, which were probably the real source of the embolus. In another case of mine there was an embolus in the left pulmonary artery, the only discoverable source of which was a large thrombus surrounding the threads of the eustachian valve. This patient, however, did not die as the result of pulmonary embolism. On the other hand, as was beautifully illustrated by Haas's case, the reticulum may ensnare an embolus reaching the right atrium from a large vein and so obviate serious pulmonary embolism. Haas's patient was a man, aged fifty-seven years, who died of cerebral embolism. There were mitral stenosis, thrombosis of the left femoral vein, and embolic infarcts of the lungs. The right atrium was dilated, and in a semilunar line surrounding the orifices of the coronary sinus and inferior and superior venae cavae were attached three groups of three or four fibrous threads each, which coalesced to form the three main threads of a network. On the net formed by the three main threads hung an embolus 6 cm. long and surrounded twice in its middle by a thread. This embolus undoubtedly came from the thrombus in the femoral vein, and one end showed the irregular surface where it had broken off. The network had ensnared this huge embolus and prevented fatal pulmonary embolism. The case reported below was similar in a general way to this case of Haas's.

REPORT OF CASE

The patient, P. L., a white man aged thirty-nine years, entered Georgetown University Hospital on Sept. 5, 1935. From June 19 until July 4, and again from August 11 until September 2, 1935, he had been a patient in another hospital. He claimed he had had pulmonary tuberculosis in 1918 and had completely recovered therefrom. For years he had suffered from severe pain in the region of the right sacroiliac joint. On June 15, 1935, he had suddenly developed precordial pain which radiated to both arms and was accentuated by exercise and deep inspiration. Examination in the first hospital did not reveal the cause of this pain. The physical examination was negative, and urinalysis, hemogram, roentgenogram of the chest, and electrocardiogram* were reported essentially normal. The temperature was elevated for a week, the highest recorded being 103° F., after which it went occasionally as high as 99.6° F. The pulse rate varied proportionally. The respiratory rate was at first moderately elevated. Although a diagnosis was not made, it is probable that the condition was acute myocardial infarction of the posterior basal region of the left ventricle.

Until his second admission to the same hospital in August, the patient was apparently well. He entered this time in order to have an operation on his back. On

*Restudy of the electrocardiogram, which was made on June 23, reveals early changes suggestive of the T₂ type of acute myocardial infarction.

the day of operation. Aug. 12, 1935, the temperature was 99.4° F., the pulse rate 64, and the respiratory rate 20. Under ethylene and ether anesthesia, partial removal of the right lumbosacral facet was done through an incision over the right posterior superior iliac spine. The operation was apparently successful since he never complained of the pain in the back thereafter. However, from August 13 until discharge an irregular fever was recorded. At times the temperature went as low as 97° F., at other times it rose as high as 103.8° F., the pulse rate varying proportionally. On August 20 he complained of a pain along the lower left costal margin. On August 22 a note was made that there was left pleural effusion with thickening of the pleura near the base. The blood pressure dropped from 120 to 96 systolic and from 80 to 68 diastolic. There was a slight cough. The respiratory rate varied from 20 to 32, but on that night it rose to 56 and then slowly decreased until nearly normal to the time of leaving the hospital, September 2. Sputum examination, agglutination tests, and other laboratory examinations were essentially normal. During the three days at home the patient had more sharp pains in the chest, now on both sides, associated with severe dyspnea. Cough with bloody sputum developed, and the temperature rose to 104° F.

On admission to the Georgetown University Hospital, Sept. 5, 1935, he presented the clinical picture of pneumonia. The temperature was 101.2° F., the pulse rate 124 and regular, and the respiratory rate 54. There were diminished tactile fremitus, marked dullness and reduced intensity of the breath sounds and a few inspiratory subcrepitant râles over both lower lobes posteriorly up to the fourth ribs, and especially in the left axilla. The blood pressure was 130 systolic and 76 diastolic. A roentgenogram of the chest made with a portable machine showed infiltration at both lung bases and possible atelectasis of the left lower lobe. Urinalysis revealed albumin, graded three-plus, hyaline and granular casts, graded one-plus, and erythrocytes, graded one-plus. A hemogram showed 79 per cent hemoglobin (Newcomer method), and the erythrocytes numbered 4,370,000 and the leucocytes 17,300 per cubic millimeter of blood. Polymorphonuclear neutrophils constituted 88 per cent of the latter. At first some blood was expectorated, but after the second day cough did not recur. Until death on Oct. 1, 1935, the course was very stormy. At one period tympanites was distressing but was relieved by injections of prostigmin and by enemas. Delirium was present most of the time. The temperature varied between 101° and 103° F., the pulse rate between 120 and 130 and the respiratory rate between 50 and 56. The cardiac rhythm was always regular, and there was never a murmur audible. The blood pressure most of the time was over 100 systolic and 65 diastolic, but the day of death it dropped to 80 systolic and 42 diastolic. On September 6 and for three days thereafter a severe pain was complained of in the right lower axillary region, but a definite pleural friction rub could not be elicited. The physical signs in the lungs progressed to those of definite areas of consolidation with numerous subcrepitant râles in both lower lobes. Dysfunction of the urinary bladder with retention of urine was troublesome for a few days. The patient was very restless and responded very poorly to sedatives and hypnotic drugs, but most of the time he ate and drank well. A second roentgenogram of the chest was reported to reveal bilateral bronchopneumonia. The hemogram did not alter much. Several blood transfusions were given, and the patient was kept in an oxygen tent intermittently. Edema of the extremities was not present at any time. Near the end moderate cyanosis appeared. The heart continued to beat, but irregularly and slowly, for several minutes after respiration ceased. Seven weeks had elapsed from the time of the operation until death occurred.

Necropsy.—Only essential findings revealed at necropsy will be recorded. There was moderate cyanosis, and the veins of the neck were distended. Upon removing the breastplate extensive and relatively recent fibrous pleural adhesions were noted in both pleural cavities. These were more dense over both lower lobes and especially

on the right side. Small subpleural hemorrhages were numerous. There was no fluid in either hemithorax. The lower lobes of both lungs were practically solid, while the upper lobes and the right middle lobe presented almost normal crepitation. On sectioning the lungs the consolidated portions were found to consist of a number of grayish, granular infarcts, about 2.5 by 4 cm. across, apparently of different ages but seemingly mostly of several weeks' duration. The pulmonary arteries of the affected lobes and of the right upper lobe were filled with emboli, some of which were apparently undergoing organization.

The heart was distended with blood, especially the right side. There were numerous subepicardial petechiae. Upon opening it by the method described and removing post-mortem blood clots a very interesting picture was revealed (Fig. 3). In the right atrium was a large embolus ensnared in a Chiari's network. The embolus,

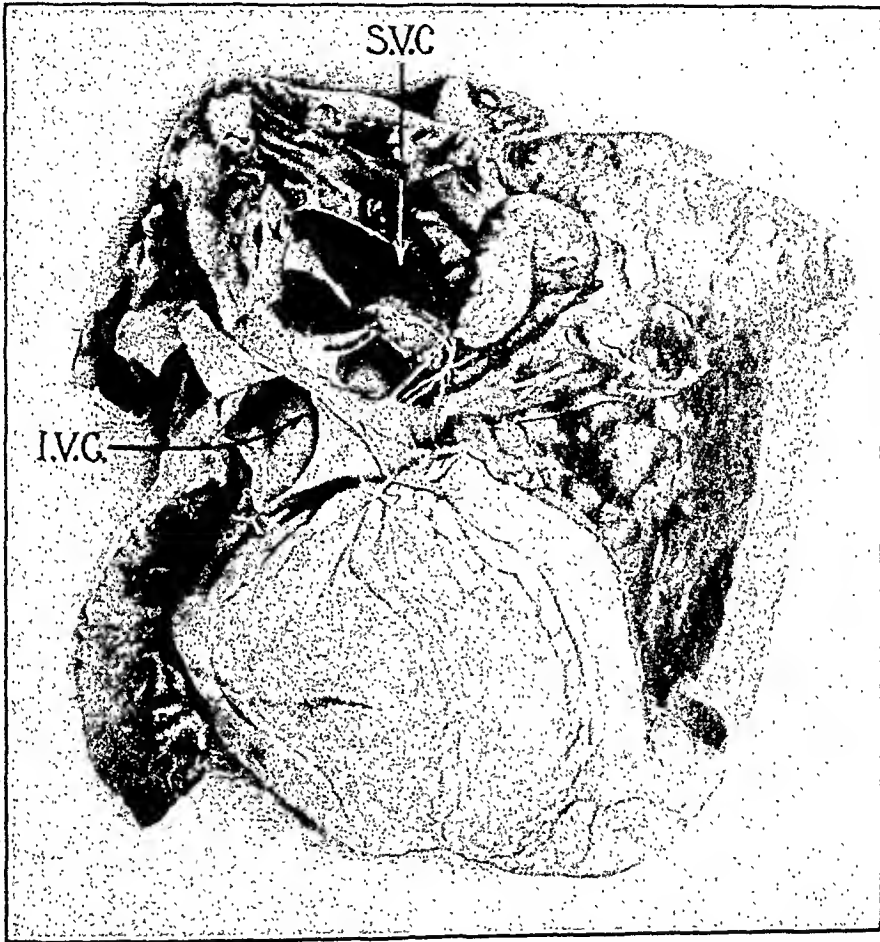


Fig. 3.—Opened right atrium and ventricle, showing the large embolus ensnared by a Chiari's network. Numerous mural thrombi are present in both the atrium and the ventricle. S.V.C., orifice of superior vena cava; I.V.C., orifice of inferior vena cava.

which was curled up like a pig's tail, was mainly grayish. It was 11.5 cm. long, and its thickness varied from 0.9 to 1.6 cm. That portion nearest the inferior vena cava for about 1.5 cm. was caught in the network. There were four sets of fibrous threads which contributed to the network. A narrow rim of thin fibrous tissue constituted the eustachian valve, which ended below in the sinus septum and continued above into a narrower rim of thin fibrous tissue which was attached to the lateral wall and roof of the atrium just medial to the crista terminalis and anterior to the orifice of the superior vena cava, medial to which it faded out in the interatrial septum. The uppermost portion of the network came from a broad expansion of the lateral portion of this rim and contributed the broadest thread of all. The next lower part of the network was derived from the eustachian valve just

anterior to the orifice of the inferior vena cava and consisted of three threads arising close together from the edge of the valve. Three more delicate threads arose from the sinus septum, the muscular ridge between the orifice of the inferior vena cava and the orifice of the coronary sinus. A few fine threads represented the thebesian valve, and an isolated one of these passed upward to join the network. The exact architecture of the network could not be determined because the threads were wrapped about and fused with the embolus. Apparently some of the threads were several centimeters long. Light grayish yellow mural thrombi of various sizes and shapes were intimately attached to the wall of the atrium. A large one on the posterior portion of the wall above the orifice of the inferior vena cava was 2 cm. in width and was elevated 1.3 cm. A large irregular one partly filled the atrial appendage. Smaller thrombi were attached to other portions of the wall. These resembled vegetations superficially. A row of these was attached to the crista terminalis, and a small one was attached to the upper thread of the network near its origin. Several small thrombi were present between the pectinate muscles. Most of these thrombi appeared to be covered by endothelium. The wall of the right atrium was definitely hypertrophied, being 0.35 cm. thick just above the atrioventricular junction. The tricuspid valve appeared normal. The right ventricle was also definitely hypertrophied and measured 0.55 cm. in its upper part. There were several large irregular thrombi projecting from the anterior and septal walls of the right ventricle, the largest ones being just below the tricuspid valve and around the so-called moderator band, which was well developed. The pulmonary valve and the main pulmonary artery appeared normal.

The coronary arteries showed significant changes. The anterior descending branch of the left was moderately sclerotic, but the lumen was not much compromised. The circumflex branch of the left for about 3 cm. was filled with a firm thrombus. Marginal branches of this artery were moderately sclerotic. The right coronary artery and its branches showed less degeneration than the left. The average thickness of the left ventricle was 1.2 cm. The myocardium appeared to be normal except for a scar in the uppermost part of the posterior wall. This scar involved the whole thickness of the wall and narrowed it in an area of about 2 by 3 cm. The left atrium, mitral valve, aortic valve, and aorta appeared to be normal.

The spleen was normal in size but very soft. It contained a small infarct under its capsule. A small Meckel's diverticulum was found, and there were two partially gangrenous appendices epiploicae with twisted pedicles. The gallbladder was the seat of cholesterosis. There were aberrant vessels to the kidneys. Otherwise the abdominal viscera were apparently essentially normal.

A search for the origin of the emboli in the heart and lungs revealed that the right femoral vein, beginning about 10 cm. from its origin, was filled with a firm, dry, red thrombus for a distance of over 15 cm. This extended into the main tributaries of the vein. The greatest part of the thrombus was not adherent to the walls of the veins, and the intima of the veins was smooth.

Microscopic study revealed that the largest mural thrombus in the right atrium was covered, in part at least, with a sheath of endothelial cells, apparently originating from the endocardium. Beneath this was a rim of delicate avascular reticulum. The thrombus was composed mainly of fibrin, the erythrocytes and leucocytes having disappeared. Scattered through the thrombus were large pale cells with ovoid nuclei. The endocardium adjacent to the thrombus was altered and contained some histiocytes and lymphocytes. The myocardium below this was essentially normal.

Sections of most of the large coronary arteries showed various degrees of sclerosis and atheromatosis. The degeneration was mainly intimal and subintimal. The lumina were not greatly compromised except in the portion of the left circumflex artery which was filled with an organized thrombus containing endothelial-lined

spaces partly filled with erythrocytes. The scar in the upper posterior wall of the left ventricle appeared to be the result of infarction. There were many thin-walled blood vessels distended with blood in portions of the scar. Sections of other portions of the myocardium did not reveal any abnormality.

Sections through several of the pulmonary arteries containing emboli showed different pictures. One embolus showed no organization although endothelium had grown around part of it. Another was well organized in its periphery, and the wall of the artery was somewhat degenerated. Still another showed greater organization. The infarcts in the lungs were typical anemic infarcts.

A section through the lower portion of the right femoral vein showed the vein to be filled with a lamellated clot, at the periphery of which was a very narrow zone of very early organization. The wall of the vein was moderately degenerated, the muscle fibers being separated and fibroblasts invading the wall in places. A smaller tributary vein was quite similar. The femoral artery showed Mönckeberg's sclerosis, with irregular deposition of calcium in the middle zone of the media. Some histiocytes were present here and there at the edge of the calcium. Sections of all other organs were of no great interest.

DISCUSSION OF CASE

Points of interest in the case were the large embolus ensnared in the Chiari's network, the numerous mural thrombi in the right atrium and right ventricle, the pulmonary emboli and infarcts, the asymptomatic femoral thrombosis, the hypertrophy of the right atrium and ventricle, the organized and canalized thrombus in the sclerotic left circumflex artery, and the scar in the upper posterior wall of the left ventricle. In the last few months of life the patient apparently had an idiopathic thrombophilia. The first thrombotic episode was probably in June, at which time it is presumed that thrombosis of the circumflex branch of the left coronary artery occurred. Recovery followed, but after the "clean" operation on his spine in August thrombosis occurred also in a large vein, probably in the right iliac or femoral. All or part of this thrombus became dislodged and was swept up to the right atrium, where a large section of it was ensnared in the Chiari's network; a section probably went also at this time to the pulmonary arteries. Other thrombi were apparently formed later in the veins but were soon dislodged and swept up to the lungs. Such an assumption seems necessary to explain the absence of symptoms and signs due to occlusion of the large veins. The asymptomatic thrombus found at necropsy in the right femoral vein and its tributaries was undoubtedly of recent origin, as indicated by smoothness of the walls of the veins and the absence of any but the earliest attempt at organization.

The large embolus entrapped in the right atrium was swished about therein and injured the endothelial lining of the atrium. This injury, together with the disturbance of the flow of blood through the atrium and the assumed thrombophilia, was responsible for the formation of the mural thrombi on its wall. Similar thrombi formed also in the right ventricle, apparently because of disturbance of blood flow in its cavity.

Some bits of these thrombi may have broken off and gone to the lungs. The course of the illness suggests also the probability of the presence of a low grade intravascular infection. The degree of toxemia and the softness of the spleen seemed to be greater than the pulmonary infarcts alone might produce. There was never any evidence clinically of cardiac dysfunction. Death resulted apparently from respiratory failure and toxemia.

The case illustrates the rapidity with which hypertrophy of the right atrium and ventricle may develop, inasmuch as the pathological investigation did not reveal any cause for the hypertrophy other than obstruction of the pulmonary arteries by the emboli, which apparently had been there only a few weeks.

SUMMARY AND CONCLUSIONS

1. Venous valves of the right atrium, the eustachian and thebesian, may be considered normal parts of the adult heart. They are remnants of the right venous valve of the sinus venosus of the embryo and serve no useful purpose in extrauterine life.

2. Chiari's network, a reticulum of fibrous threads in connection with these valves with attachments to the crista terminalis and tuberculum loweri, occurs probably in from 2 to 3 per cent of otherwise developmentally normal hearts.

3. Chiari's network produces no symptoms or signs.

4. This network may be the origin of thrombi which may give rise to pulmonary emboli, or it may ensnare emboli from some systemic vein and prevent sudden fatal pulmonary embolism (the paradox of Chiari's network).

5. A case is reported in which death eventually occurred from embolic pulmonary infarcts and low grade infection and in which a Chiari's network had ensnared an embolus 11.5 cm. long originating from an asymptomatic thrombus which had formed in a large vein. The patient apparently had a thrombophilia, since he had just previously had coronary arterial thrombosis and also later developed mural thrombi in the right atrium and ventricle. The case illustrates the rapidity with which hypertrophy of the right atrium and ventricle may occur.

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AURICULOVENTRICULAR DISSOCIATION AND THE ADAMS-STOKES SYNDROME IN ACUTE CORONARY VESSEL CLOSURE*

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THE purpose of this study is to call attention to the clinical course and the graphic manifestations of a consecutive series of fifteen patients who developed auriculoventricular dissociation and the Adams-Stokes syndrome following acute coronary vessel closure. The Adams-Stokes syndrome may be defined as a clinical condition characterized by recurrent attacks of unconsciousness, lasting from eight seconds to several minutes, associated with epileptiform convulsions and stertorous breathing and ending in apnea. During such periods there is a collapse of the circulation with a drop in the blood pressure and absence of the pulse and heart sounds. The term was coined by Huchard¹ who gives credit to both Stokes² and Adams³ for having described the clinical picture in the presence of bradycardia. Burnett⁴ and Pletnew,⁵ however, cite Morgagni⁶ as the first to have observed the phenomenon.

We now know, from an increasing number of carefully correlated observations, that syncopal seizures in patients in whom alterations in the cardiac mechanism are responsible for such attacks may be due, in the main, to (a) stoppage of the whole heart, that is, absence of both auricular and ventricular contractions from direct or reflex stimulation of the nodes of the heart through the vagus or carotid sinus⁷⁻¹⁰; (b) sudden interference with impulse formation in the auriculoventricular node¹¹⁻¹³; (c) cessation of ventricular contractions in the presence of persistent auricular activity during complete heart-block¹⁴; and finally (d) the various grades of acceleration of the ventricles that end in transient periods of ventricular fibrillation or flutter.¹⁵

Mahaim's¹⁶ recent excellent survey of the literature and Geraudel's¹⁷ microscopic studies reveal that the Adams-Stokes syndrome occurs most commonly during auriculoventricular dissociation in the course of the more gradual form of ischemia to the auriculoventricular node of the heart, as a result of arteriosclerotic narrowing of the blood supply to this specific tissue. With the exception of some sporadic observations,¹⁸ a systematic study of the Adams-Stokes syndrome and the outcome of such patients in the course of a sudden closure of a coronary artery is still wanting. A knowledge of the circulation of the node is essential to an understanding of this problem.

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THE CIRCULATION TO THE CONDUCTION MECHANISM OF THE HEART

The auriculoventricular conduction mechanism of the heart consists of a node (Tawara) and a bundle (His) of neuromuscular tissue which bifurcates into two main branches in the region of the upper part of the interventricular septum. The right limb breaks up into an extensive interlacing and interanastomosing network of fibers which are distributed over the internal surface of the right ventricular wall. The left limb passes over the top of the interventricular septum and spreads into a fan-shaped, thin and flat structure and distributes itself over the interior surface of the left ventricle.¹⁹

The circulation to the auriculoventricular node has its origin in the anterior and posterior interventricular arteries, the former originating from the left coronary and the posterior interventricular from the right coronary. The anterior interventricular artery has its origin in the region where the left coronary bifurcates to give off the circumflex branch of the left, but the posterior cannot be so easily distinguished since it is a continuation of the right circumflex artery.

In approximately 90 per cent of human beings¹⁹⁻²³ the right circumflex branch of the right coronary artery crosses the crux posteriorly and in that region gives off the *ramus septi fibrosi*, which supplies the superior portion of the interventricular septum and sends a branch into the auriculoventricular node, coursing along this as far as the main bundle and the upper part of both bundle branches. Usually, therefore, it is the right coronary artery which furnishes the nutrition for the main portion of the auriculoventricular node, but exceptions are not rare, and the left coronary artery occasionally sends its branches posteriorly to the superior interventricular septal region and in that manner, crossing the crux, becomes the main supply to the node (10 per cent of cases). Nevertheless, the vascularization of the auriculoventricular node may be said to be most usually posterior, no matter from which of the coronary arteries the blood supply originates.

The left branch of the bundle has a double arterial supply. Its anterior ramifications are supplied by a large number of perforating branches from the anterior descending branch of the left, while its posterior ramifications receive their nutrition from the less numerous posterior perforating branches of the right coronary artery.

The right bundle branch, however, receives most of its supply from the anterior perforating branches of the large descending branch of the left. Gross has described a special artery supplying the right bundle branch and has called this the *anterior ramus libri dextri*. According to Cranicianu, in its first portion, the right bundle branch receives its vessels from two superior anterior perforating arteries. In its second portion it is supplied by the same artery as described by Gross, while in its third portion there are additional arterioles which anastomose in this inferior region with arterioles originating in the right coronary.

There is a unanimity of opinion that the sino-auricular node is supplied from the right coronary artery in approximately 60 per cent of the cases and from the left in 40 per cent. The existence of anastomoses between the anterior and posterior perforating arteries of the septum and consequently between the two arteries supplying the auriculoventricular conduction mechanism is well established from anatomical studies.

With these points in view, the following case histories are presented out of a series of fifteen patients with acute coronary vessel closure and Adams-Stokes seizures that I have seen during the past few years. They give an idea of the onset of the symptoms, the clinical course, and the treatment for most of such patients in the course of their illness.

REPORT OF CASES

CASE 1.—L. B., a male, aged sixty-five years, was known to have had hypertension for six years. On Feb. 18, 1935, while sitting in the bathroom, he had a sudden seizure of unconsciousness with convulsions. During the next fifteen minutes until he was seen by a physician, he had several other seizures of stertorous breathing with unconsciousness. In one of these attacks he bit his tongue badly, for when seen he was bleeding from the mouth. His face was intensely cyanotic. His respirations were very irregular. Long periods of apnea alternated with Cheyne-Stokes respirations. His skin was cold and clammy. His heart rate varied between 6 and 46 beats per minute. The heart sounds were barely audible. The lungs were full of moisture. The liver and spleen were not palpable. He was incontinent of feces and of urine. The blood pressure was not obtainable.

Electrocardiograms obtained at this time revealed low voltage, left axis deviation, prominent Q-waves in Leads II and III, and R-T fusion above the isoelectric line in Leads II and III. The ventricular complexes were aberrant in all three leads. The ventricular rate was regular and averaged 38 beats per minute, the auricles beating twice as fast.

The administration of atropine sulphate (gr. 1/75) resulted within seven minutes in an acceleration of the ventricular rate to 76 beats per minute. The further administration of a similar dose resulted in clearing up the moisture in his lungs. Three hours after the onset of his first attack his ventricular rate gradually became lower until, when it reached a level of about 12 to 16 beats per minute, the patient suffered again from an Adams-Stokes seizure. At this time epinephrine hydrochloride (1 c.c. of the 1:1000 solution) was injected intramuscularly and within three minutes there was a return to a regular rhythm, with the ventricles beating at 78 per minute.

Aside from warmth to the body and the administration of hot liquids, the patient received no other medication. Electrocardiograms obtained on the following morning revealed a Q-T₂, Q-T₃ pattern with marked inversion of the T-waves in all three leads, and this pattern has persisted to the present day.

The patient was kept in bed for six weeks and advised to take a prolonged rest until he was enabled to walk without suffering any signs of shortness of breath. His blood pressure at present is 130/80, and he is up and about, carrying on his work as a normal individual.

CASE 2.*—A. C. G., a male, aged seventy-one years, was known to have had hypertension for at least five years. On March 22, 1931, at 3:00 A.M. he complained of

*I am indebted to Dr. Joseph Levy, of New Rochelle, N. Y., for the electrocardiograms of this patient.

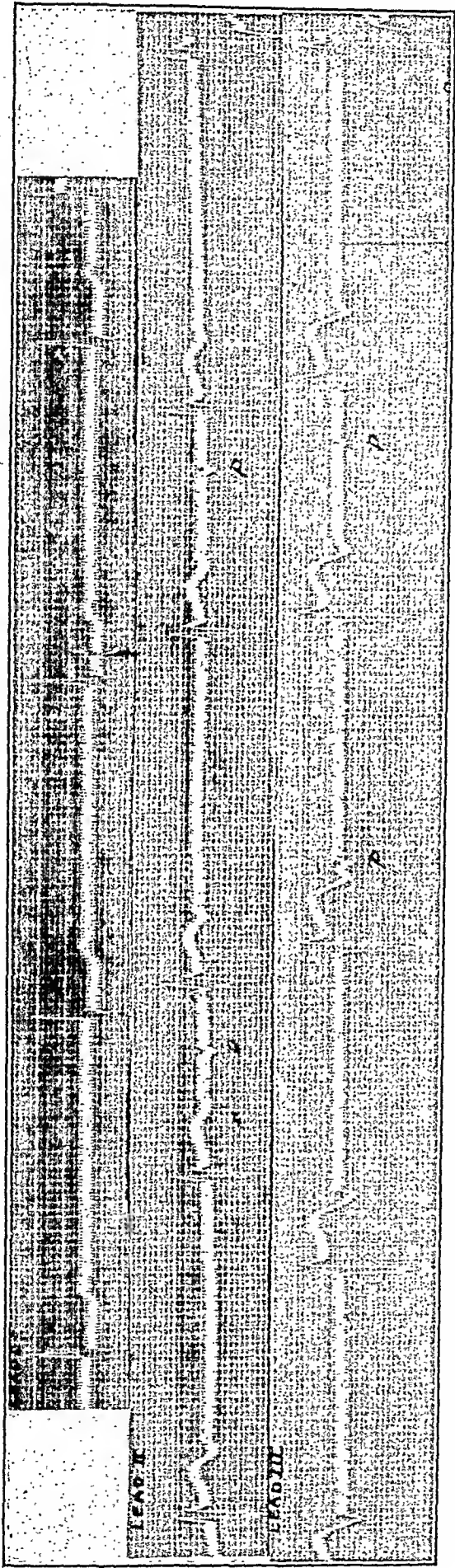


Fig. 1.—An electrocardiogram obtained shortly after and prior to a syncopal attack following an acute coronary vessel closure. Note the irregularity of the ventricles, the slow ventricular rate, and the almost total absence of auricular complexes.

nausea and of pain over the precordial region radiating to the left arm, and he vomited. His blood pressure had dropped from 230/110 to 100/82. Several hours later he became very restless, complained of excruciating pains over the entire chest and developed Cheyne-Stokes respiration. Then he suddenly lapsed into unconsciousness with epileptiform convulsions.

Electrocardiograms obtained at this time and shortly before a major seizure of unconsciousness showed left axis deviation with some slight intraventricular conduction disturbance. Q_2 formed the main ventricular deflection, and in Lead III there was R-T fusion above the isoelectric line. The ventricular rate was totally irregular, the rate varying between 20 and 40 beats per minute, and there was only an occasional P-wave present in the record (Fig. 1).

The injection of atropine sulphate (gr. 1/75) on the following day eliminated the block and accelerated both the auricles and the ventricles, but only for very short periods. Twenty-four hours before death, which occurred three days after the first episode, there was stoppage of the whole heart for periods of from twenty to forty seconds, with typical Adams-Stokes seizures. The repeated administration of epinephrine hydrochloride (1 c.c. of the 1:1000 solution) yielded a slight acceleration of the ventricular rate but did not prevent recurrences of the syncopal attacks. The patient was desperately sick as he would go from one attack into the other, and no medication seemed to be of any avail. He died in pulmonary edema three days after the onset of his acute coronary vessel closure. No autopsy was obtained.

CASE 3.—M. W. C., an insurance broker, aged sixty-four years, was first seen on the morning of Aug. 6, 1932, at his office, where he was found on the floor in a semistuporous condition. He had been having repeated convulsions, with frothing at the mouth, for about twenty minutes before the arrival of a physician. Examination at this time showed him to be in a semistuporous condition, intensely cyanotic, with blood-tinged froth oozing from both the nares and the mouth. His breathing was irregular. The superficial veins of his neck were markedly distended, and as he was being examined, there were occasional convulsive movements of his left arm, forearm, and face. His eyes had a glassy stare, but he could be easily aroused by supraorbital pressure. The apical impulse of his heart was neither visible nor palpable. The blood pressure was 134/98 and his lungs were full of large bubbling râles. The heart rate was totally irregular and averaged between 16 and 40 beats per minute when counted over a period of several minutes.

An electrocardiogram, obtained while the patient was still on the floor, revealed an irregular slow ventricular rate, averaging 28 beats per minute with auricular fibrillation. The main ventricular deflections showed low voltage, marked intraventricular conduction disturbance, and a tendency toward right axis deviation. This type of complex persisted for the rest of his life (Fig. 2).

On the assumption that the auricles were beating independently of the ventricles at this time because of the slow ventricular rate, even though the rhythm was totally irregular, the patient was given 1 c.c. of epinephrine hydrochloride (1:1000 solution), and within five minutes there was an acceleration of the ventricular rate to 68 beats per minute. The rhythm, however, still remained irregular and auricular fibrillation persisted.

Following this increase in the heart rate, the patient became conscious and could talk coherently. He was removed to his home, put to bed and given hot drinks. His body was kept warm with hot water bottles and warm blankets and he received an injection of atropine sulphate (gr. 1/75) for the relief of his pulmonary edema.

Two hours after his initial seizure, when the heart rate had again returned to a level of 27 beats per minute, he was given another injection of epinephrine hydrochloride (1 c.c. of the 1:1000 solution), and again there was an acceleration of the heart rate to an average of 70 beats per minute.

He received a total of 7 c.c. of epinephrine hydrochloride in a period of seven hours, the injections being given whenever he complained of dizziness or faintness. As a rule, these symptoms invariably coincided with the reduction in his heart rate below 25 beats per minute.

Following that, no other medication was necessary for the next two days. He was then placed on ephedrine sulphate in doses of 30 mg. twice a day and this was increased to three times a day when it was noted that the ventricular rate vacillated

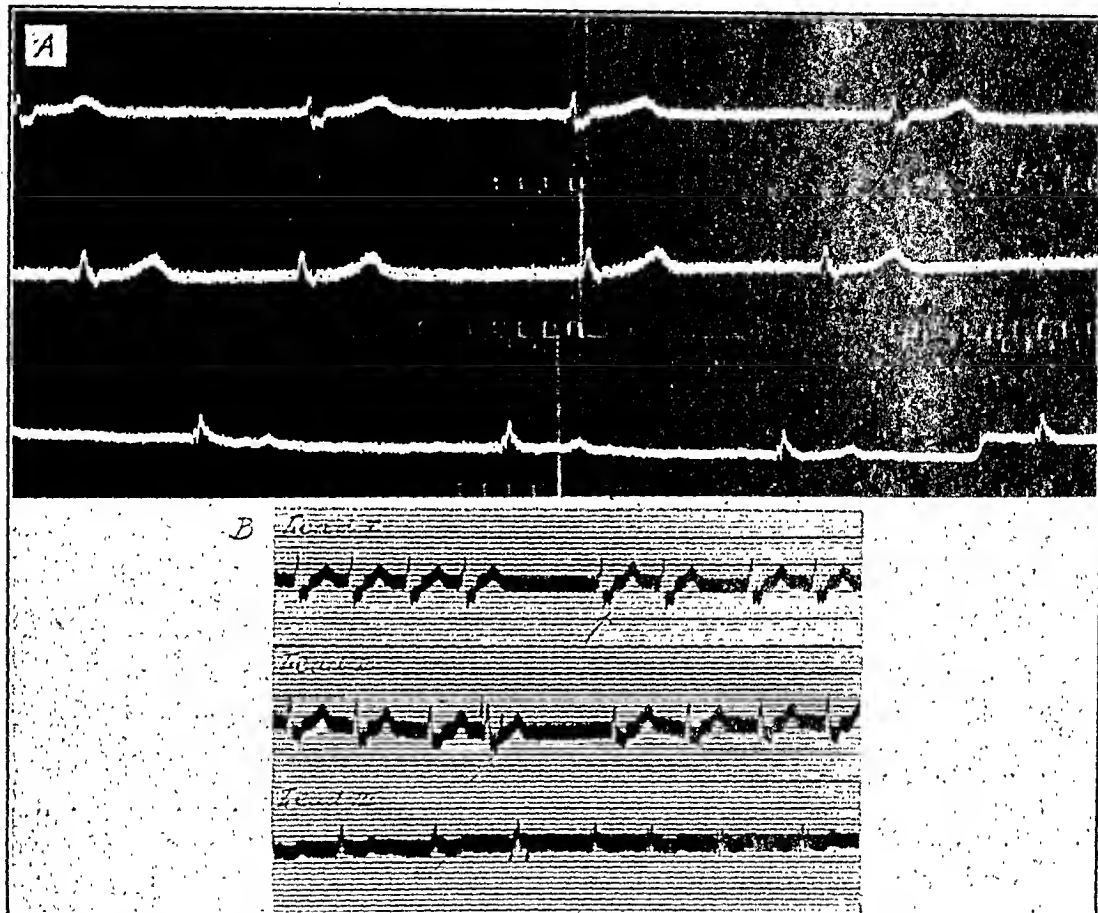


Fig. 2.—A, auricular fibrillation with a slow ventricular rate following an acute coronary vessel closure.

B, an increase in the ventricular rate obtained by the administration of epinephrine hydrochloride. Note the intraventricular conduction disturbance in both records.

between 22 and 29 beats per minute. On three doses of this drug per day, his heart rate for the next six weeks averaged about 45 beats per minute. The auricular fibrillation persisted.

Within eight weeks following his initial Adams-Stokes seizure, the patient was out of bed and up and about. His heart sounds were now audible. The blood pressure was 140/65. Fluoroscopic examination of his chest revealed his left ventricle to be concentrically hypertrophied and unusually large. His lungs were moderately congested. The edge of the liver was 6 cm. below the costal margin in the region of the midclavicular line. For the next two years until his death on April 7, 1935, he had recurrent Adams-Stokes seizures only when he omitted the ephedrine from his daily routine. On several occasions when he was studied, omissions of this drug for a period of ten days was followed invariably by a lowering

of the ventricular rate in the presence of auricular fibrillation followed by a syncopal seizure. For his congestive heart failure, he received periodic injections of salyrgan intramuscularly and this, in addition to a salt-poor diet with moderate rest, was sufficient to keep him comfortable. He died suddenly one day while he was walking on the street.

CASE 4.—L. L., a tailor, aged fifty-six years, was first seen on Feb. 9, 1933. About twenty minutes earlier, he had been found in a semistuporous condition on the floor of his shop. He was known to have had high blood pressure for seven years but never complained of any symptoms referable to his heart. When seen shortly after his accident, he was extremely cyanotic, and his respirations were irregular. He was disoriented, and his speech was quite unintelligible. His skin was moist and cold. His pulse was barely palpable. His heart sounds were hardly audible and his systolic blood pressure was 90. The diastolic level could not be obtained even though his ventricular rate was 62 beats per minute at that time.

While being examined on the couch approximately one-half hour after his attack, he suddenly stiffened out, with his hands outstretched and his fists taut. His head turned toward the left, his eyes rolled, his face assumed a pasty pallor, and there were several convulsive movements of his head in the direction opposite the rolling of his eyes. He lost consciousness, stertorous breathing set in, he was incontinent of feces and of urine, and his heart sounds, although barely audible, could still be heard beating at the average of 10 per minute.

An electrocardiogram obtained shortly after this episode revealed left axis deviation, marked intraventricular conduction disturbance, complete auriculoventricular dissociation, with a ventricular rate averaging 35 beats per minute, and the auricles beating irregularly and varying between 40 and 60 beats per minute.

The patient was given 1 c.c. of epinephrine hydrochloride (1:1000 solution), and within five minutes following the injection there was a return to normal rhythm. He became rational and was transferred home. His rhythm remained normal for a period of eight weeks, during which time he received ephedrine sulphate (30 mg.) once a day. When he was given more than this dose per day, he developed systemic manifestations, such as tremors and sweating, so that his dose had to be reduced to the lowest possible level.

After ten weeks, he was up and about and became conscious of an occasional omission of a heartbeat. Electrocardiograms obtained at such a time showed an omission of a complete ventricular cycle. Shortly afterward he developed 2:1 heart-block, with a ventricular rate of 40. It was possible to abolish this with ephedrine sulphate, but he never felt well when his heart was in normal sinus rhythm again. At present, he is up and about, perfectly comfortable on 30 mg. of ephedrine sulphate once a day. On several occasions when he was admitted to the Montefiore Hospital for study, it was possible to demonstrate a very definite relationship between the omission of the drug and a further reduction in the ventricular rate. Whenever the ephedrine was omitted, his heart rate fell below its basic level of 38 beats per minute and he began to complain of dizziness with spots before his eyes. Indeed, on one occasion he developed an Adams-Stokes seizure when the ephedrine sulphate had been omitted for five consecutive days.

Throughout his entire illness, the patient never showed signs of congestive heart failure, such as shortness of breath, enlargement of the liver, or edema of the lower extremities.

CASE 5.—S. G., a clothing salesman, aged fifty-three years, was admitted to the Montefiore Hospital on May 9, 1930, and died on Dec. 20, 1934. His main presenting complaints on admission were associated with a tumor involving the spinal cord in the region of the first down to the level of the fourth dorsal vertebra. He was bedridden most of the time and had no symptoms referable to his heart

until March 2, 1934, at 5:30 P.M. On that afternoon, the patient was seen in a drenching sweat shortly after he had had an attack of projectile vomiting. He said that "things went suddenly black" before his eyes and he had a very severe "inward pressure" below the sternum. He had lost consciousness shortly after

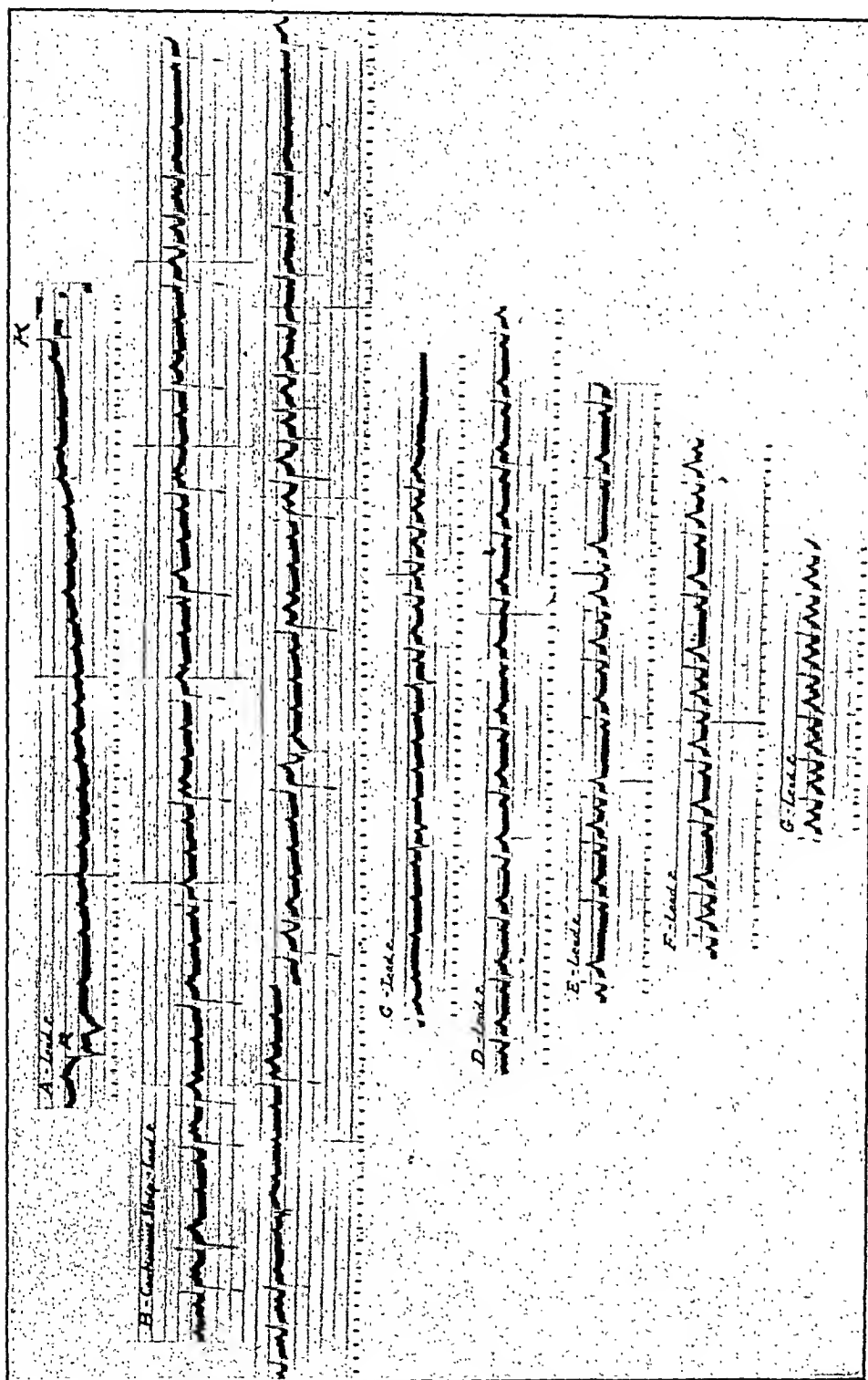


Fig. 3.—A, electrocardiograms showing standstill of the ventricles following an acute coronary vessel closure. B, a record obtained after the injection of 1 c.c. of the 1:1000 solution of epinephrine hydrochloride. Note the acceleration of the ventricular rate following the injection of the drug, with runs of tachycardia alternating with bradycardia before the final establishment of a normal rhythm, G.

that and when seen his peripheral and apical heart rates averaged 28 beats per minute. His blood pressure was 70/40.

While being examined at this time, his heart became progressively slower until it reached a level as low as 6 beats per minute, when the patient again lost consciousness, developed stertorous breathing, became intensely cyanotic, had repeated convulsions, and was incontinent of feces and of urine. Shortly after this unusually

slow ventricular rate of only 5 to 6 beats per minute, the heart rate suddenly became accelerated to 64 beats per minute. For the next half hour he had several typical Adams-Stokes attacks with a marked reduction in the ventricular rate during which time repeated electrocardiograms were obtained of his abnormal cardiac rhythm (Fig. 3).

Following one of these typical attacks of ventricular standstill, the patient was given 1 c.c. of epinephrine hydrochloride (1:1000 solution) and within a minute following the injection, the blood pressure rose to 142/60, and his heart rate was accelerated to 50 beats per minute, but the rhythm was irregular. Following another injection of epinephrine hydrochloride about ten minutes later, his blood pressure rose to 200/70, but his heart rate returned to a normal sinus rhythm after successively going through variable interferences with the conduction mechanism.

For the next few days his temperature was elevated to 101° F., and he suffered several more attacks of syncope associated with epileptiform convulsions, until March 19, 1934, when his apical rate was 60 beats per minute. From then on until the day of death on Dec. 20, 1934, he had normal sinus rhythm.

Autopsy revealed his heart to be markedly enlarged, weighing 520 gm. The pericardial layers were smooth and shiny. The pericardial sac contained 800 c.c. of clear yellowish fluid. On the posterior surface of the left ventricle there was a marked depression in the wall consisting of fibrous tissue. The ventricular walls were thickened, especially in the region of the pulmonary conus. The myocardium of the anterior surface of the left ventricle showed numerous scattered, white, fibrous areas. The coronary arteries were markedly narrowed and presented areas of calcification, but the circumflex branch of the left showed only a tiny pinpoint lumen that led to the infarct on the posterior wall of the left ventricle and the adjacent septum in the region of the auriculoventricular node and its bundle.

CASE 6.—C. T., a male, aged sixty-nine years, was admitted to the Montefiore Hospital on Oct. 22, 1931, and died on May 11, 1932. He was known to have had a blood pressure of 280/70 at the Presbyterian Hospital where he had been on several previous occasions in 1929 because of dyspnea, dizziness, swelling of the ankles and abdomen, and vomiting of seven weeks' duration. During one year prior to his admission to the Montefiore Hospital he had been complaining of recurrent precordial pains. In August, 1929, he fainted on the street and, when seen one-half hour after his accident, his heart rate was found to be 16 beats per minute. An electrocardiogram obtained at that time showed marked intraventricular conduction disturbance, right axis deviation, complete auriculoventricular dissociation, with the ventricles beating irregularly and varying between 16 and 28 beats per minute. The auricular rate was regular.

The administration of epinephrine hydrochloride (1 c.c. of the 1:1000 solution) forty minutes following his attack of unconsciousness was associated with a return of the heart rate to 60 beats per minute, and this persisted for several months thereafter. He required repeated doses of diuretics for relief of his congestive heart failure and then finally, because of recurrent attacks of syncope during which his heart rate would fall to a level of 6 to 8 beats per minute, he was admitted to the Montefiore Hospital.

Here it was possible to accelerate his heart rate very readily with epinephrine hydrochloride, but only temporarily. The administration of this drug would invariably produce marked systemic manifestations, even in small doses of 0.25 c.c. of the 1:1000 solution, with a concomitant increase in his heart rate far above the basic level.

He was likewise intolerant of ephedrine, and its administration was invariably followed by precordial pain with an irregular ventricular rate which resembled

very closely the cardiac abnormalities seen to follow the injection of epinephrine in this patient. He died in congestive heart failure, with complete auriculoventricular dissociation.

Autopsy revealed that his heart weighed 550 gm. There were a few pleuro-pericardial adhesions. There was marked hypertrophy and some dilatation of the left ventricle. The anterior and posterior papillary muscles were flattened and grayish in color. On section they appeared yellowish brown. The mouths of the

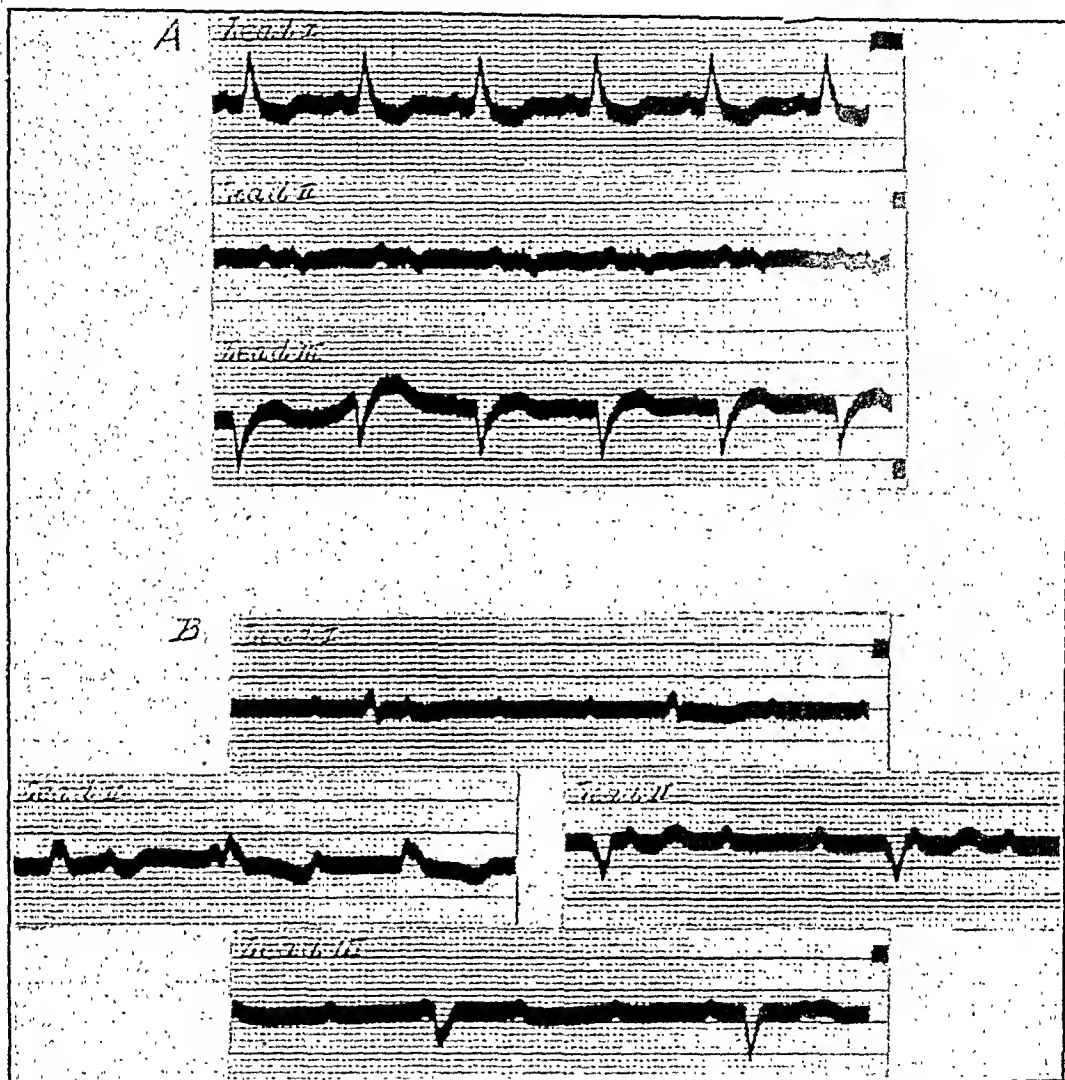


Fig. 4.—A, an electrocardiogram showing intraventricular conduction disturbance as a result of myocardial infarction, prior to another acute coronary vessel closure with Adams-Stokes seizures.

B, an electrocardiogram of the same patient obtained after an acute coronary vessel closure with Adams-Stokes seizures. Note the complete auriculoventricular dissociation, the lowered voltage, the irregular ventricular rate, and the change in the direction of the complexes in Lead II.

coronary arteries were patent. There was marked subendocardial fibrosis of the left and right ventricles. The posterior wall of the left ventricle showed a fairly extensive area about 3 cm. in length, extending through the entire thickness of the myocardium which was grayish yellow in appearance and which was adjacent to an area somewhat reddish in color that looked like a comparatively recent infarct. There was marked atherosclerosis of the descending branch of the left coronary artery. The lumen, however, was patent throughout. The transverse branch of the left coronary artery showed very marked thickening; one portion of the lumen was practically pinpoint in size, and its center was filled with a gelatinous pale gray substance which, on section, turned out to be a recanalized thrombus. The right coronary artery showed no actual occlusion.

DISCUSSION

It is very obvious from these observations that syncopal attacks and complete heart-block are much more commonly associated with an acute coronary vessel closure than has been considered hitherto (Table I). Of the fifteen patients in this series, there were thirteen males and two females; the youngest was fifty-four years and the oldest seventy-one years of age. Each one was known to have had hypertension for a considerable time prior to the development of the acute coronary vessel

TABLE I

SHOWING THE AGE, SEX, ANTECEDENT HISTORY AND ELECTROCARDIOGRAPHIC PATTERNS OF 15 PATIENTS WITH ACUTE CORONARY ARTERY CLOSURE AND THE ADAMS-STOKES SYNDROME

NAME	SEX	AGE	ANTECEDENT HISTORY	E.C.G. FOLLOWING ACUTE CORONARY VESSEL CLOSURE	DURATION OF LIFE AFTER THE ONSET OF ADAMS-STOKES SYNDROME	THE RESTORED CARDIAC RHYTHM
L. B.	M.	65	Hypertension	L.A.D. Low Voltage Q ₂ , Q ₃ Pattern	Living	Sinus rhythm
L. L.	M.	56	Hypertension	R.A.D. Low Voltage I.C.D.*	Living	Complete heart-block
B. S.	F.	58	Hypertension	L.A.D. Q ₂ Pattern	Living	Sinus rhythm Transient heart-block
S. L.	M.	68	Hypertension C.H.F.†	Low Voltage I.C.D.	Living	Sinus rhythm
A. L.	M.	58	Hypertension	L.A.D. Low Voltage A.F.	20 months	Sinus rhythm
M.W.C.	M.	64	Hypertension C.H.F.	R.A.D. Low Voltage A.F.	33 months	A.F. Transient heart-block
L. D.	M.	68	Hypertension C.H.F.	R.A.D. Low Voltage I.C.D.	28 months	Sinus rhythm
S. G.	M.	53	Hypertension	L.A.D. I.C.D.	10 months	Sinus rhythm
C. T.	M.	69	Hypertension C.H.F.	R.A.D. I.C.D.	25 months	Sinus rhythm Transient heart-block
F. L.	M.	54	Hypertension	L.A.D. A.F.‡	24 months	Sinus rhythm
F. M.	M.	68	Hypertension	R.A.D. I.C.D.	22 months	Sinus rhythm
R. N.	M.	63	Hypertension Diabetes	L.A.D. Low Voltage I.C.D.	4 days	
S. S.	M.	58	Hypertension	L.A.D. Q ₂ , Q ₃ Pattern	3 days	
A. C. G.	M.	71	Hypertension	L.A.D. Q ₂ Pattern	4 days	
B. F.	F.	62	Hypertension	R.A.D. I.C.D.	6 days	

*I.C.D., intraventricular conduction disturbance.

†C.H.F., congestive heart failure.

‡A.F., auricular fibrillation.

closure, and six showed signs of congestive heart failure, presumably from previous myocardial infarcts. Aside from the well-known symptoms and signs that follow a coronary vessel closure, such as precordial pain, shock, vasomotor collapse, fever, leucocytosis, drop in the blood pressure, weak heart sounds, pulmonary edema, and Cheyne-Stokes respiration, they all exhibited, in addition, the Adams-Stokes syndrome.

The auriculoventricular node of the heart over which impulses are transmitted from the auricles to the ventricles is an unusually sensitive structure. Sudden interference with the circulation to this conductive mechanism may result in a disruption of the normal sequence of events from the auricles to the ventricles. The ventricles may suddenly stop contracting before they assume an independent pacemaker of their own. In that event the absence of an adequate cerebral circulation from stoppage of the ventricles may result in an Adams-Stokes seizure, the duration of which will depend upon the periods of ventricular standstill.

Since posterior infarcts in the region of the auriculoventricular node are almost as frequent as anterior infarcts, judging from personal observations on one hundred consecutive patients with coronary artery closure that have come to necropsy at the Montefiore Hospital, it is likely that this mechanism of standstill of the ventricles explains the coma that is so often seen in patients with acute coronary artery closure. Occasionally the auriculoventricular dissociation is of only short duration, varying from a few minutes to several days, depending on whether the artery to the node itself is occluded or whether the node is the seat of an inflammatory reaction from closure of larger radicals away from it. Again there may be an extension of a thrombus from the septal artery to the artery of the bundle, and the block and syncopal attacks may appear a few hours or a few days after the coronary vessel closure.

Repeated syncopal seizures result in a cerebral anoxemia which may so depress the brain centers that after several attacks within only a few minutes, patients remain unconscious for long periods at a time. Indeed, I have seen patients with syncopal attacks from other causes of stoppage of the circulation, stay in coma for as long as twelve hours, despite the return of the basic heart rhythm and rate to normal figures.

As a rule, the size of the posterior infarcts of the left ventricle of the heart are smaller than those of the anterior infarcts. The vessels supplying that region are not of the caliber of those anteriorly. Since most patients exhibiting syncopal attacks apparently recover from their initial accident following closure of the vessels posteriorly, it becomes apparent that such lesions in this region are not so grave as those in other localities of the heart, despite the severity of the symptoms. With increasing age and with the antecedent hypertension which almost all of these patients present, there develops a concomitant diminution in the caliber of the vessels supplying this region of the heart, from the intimal proliferation of the arteriosclerotic process that accompanies the hypertension. It is a gradual narrowing that thus prepares the soil for the

final closure of the artery to the node so that the heart is able to tolerate the trauma much better than if such a process were not there. The smaller the size and caliber of the vessels occluded, the less severe the trauma and the shock.

It seems to me that this is a much more plausible explanation for the recovery of these patients than the development of increasing anastomoses which are described as present in the progressively ageing heart.¹⁹ These anastomoses to the arteries supplying the auriculoventricular node and the bundle in themselves undergo changes in structure similar to those of the main supply of the vessels which are usually occluded, and it is hardly possible to expect them to function through the infarcted area which surrounds the bundle and the conducting mechanism following the closure of the main vessel. Furthermore, since the heart-block persists for some time in the majority of patients who survive the initial shock and trauma, it is very obvious that once the arterial supply is completely occluded and the idioventricular pacemaker assumes a function of its own, it is only when recanalization takes place and the node itself is nourished again by the original arterial supply that normal rhythm is resumed.

I have had the opportunity recently to confirm this belief in a patient who showed heart-block for four years. During all this time the main ventricular deflections of the electrocardiogram were aberrant and resembled those seen in a so-called arborization block. Shortly prior to death she developed normal sinus rhythm, again with complexes of the supraventricular form.

At necropsy the main artery to the bundle which had been thrombosed, showed almost complete recanalization, but the surrounding arterioles entering the region of the bundle were completely obliterated by intimal thickening. The presence of a few fibers in the neuromuscular tissue which had still escaped degeneration by receiving a new blood supply through the recanalized vessel enabled the heart to resume normal sinus rhythm. My own observations on hearts with multiple myocardial infarctions reveal a remarkable absence of anastomosing vessels in the infarcted regions following coronary artery closures. The heart must be nourished in another manner than through anastomoses, or perhaps it does not require as much nourishment in its infarcted state as it does normally. Obviously, the margin of safety is very great. Otherwise we should not have such long survivals of patients with multiple myocardial infarctions of the heart.

THE ELECTROCARDIOGRAM IN PATIENTS WITH COMPLETE HEART-BLOCK AND ADAMS-STOKES SEIZURES FOLLOWING AN ACUTE CORONARY VESSEL CLOSURE

Our conception of the relationship between the arterial supply to the heart, the underlying pathological lesion, and the graphic manifestations noted in the electrocardiogram has changed considerably since

Ball¹⁶ summarized the available literature on the electrocardiograms seen in heart-block following an acute coronary artery closure. We now have sufficient evidence at hand to believe that the electrocardiogram can localize for us the infarcted area in either the anterior or the posterior wall of the left ventricle, regardless of which of the coronary vessels of the heart is occluded.^{24, 25, 26}

For such localizations of an infarct it is essential that the main ventricular deflections of the electrocardiograms be of the supraventricular form. They must not show any aberration associated with intraventricular conduction disturbance, either before or after the development of heart-block. Indeed, in the present state of our knowledge, all such records must be excluded when correlation is made between the infarcted area and a specific electrocardiographic pattern. On such a basis, since thirteen of the fifteen patients reported in this study showed marked intraventricular conduction disturbances in the electrocardiogram before, during, and subsequent to an acute coronary artery closure, the records are valueless in localizing either the vessels occluded or the areas in the ventricles that have been infarcted.

On the other hand, it has been pointed out in the anatomical description of the vascular supply to the bundle that no matter which artery supplies the posterior wall of the left ventricle, heart-block invariably results from a closure of a vessel posteriorly. It is therefore fair to conclude, from studies so far, that the presence of Adams-Stokes seizures with dissociation of the auricles from the ventricles results, as a rule, from infarction posteriorly, no matter whether the arterial supply to the conduction mechanism originates from the right or the left coronary artery. The presence of heart-block of this type, then, is of itself enough to localize the lesion in the heart for us, independent of the form, shape, or size of the ventricular deflections and of the T-waves which may follow them.

The autopsy findings in two of our patients support this contention. In both instances, for example, it was the circumflex branch of the left coronary artery that crossed the crux posteriorly in the region of the interventricular septum and supplied the auriculoventricular conduction mechanism. In both instances branches of that artery were occluded and yielded posterior wall infarctions in the region of the interventricular septum and auriculoventricular node. Yet the electrocardiograms showed marked aberration of the ventricular complexes, and because of that the pattern usually associated with posterior infarctions was totally masked. Nevertheless, since both patients showed standstill of the ventricles with the clinical manifestations of acute coronary artery closure and heart-block, the pathological lesion was localized posteriorly on purely anatomical grounds.

A note should be made here of the auricular complexes in the electrocardiograms and the auricular rhythm present shortly after the on-

set of the syncopal attacks and following the acute coronary artery closure in the posterior region of the left ventricle. In one patient (Fig. 1) there was almost a total standstill of the auricles for long periods at a time, only one or two auricular complexes appearing to every six ventricular beats. In several others, auricular fibrillation set in both the transient and the permanent forms. There can hardly be any relationship between these arrhythmias of the auricles and an involvement of the artery supplying the sino-auricular node. Since in normal hearts this sinus node is supplied in 60 per cent of the instances by a stout branch arising in the right coronary artery, one would assume that the changes in the auricular behavior of our patients might be the result of obstruction to the arterial supply to the sinus node. This, however, is a very remote possibility. I have repeatedly seen such changes in the rhythm of the auricles following the asphyxia that results from stoppage of the ventricles. Every type of auricular irregularity may then occur, such as flutter, fibrillation, and tachycardia without any organic changes in the arterial supply to the sinus node. In the majority of all patients such changes in the behavior of the auricles are only transitory and appear after the syncopal attacks, but disappear after resumption of the basic ventricular rhythm.

THE USE OF EPINEPHRINE HYDROCHLORIDE AND EPHEDRINE SULPHATE IN
THE TREATMENT AND PREVENTION OF SYNCOPAL ATTACKS FOLLOWING
AN ACUTE CORONARY VESSEL CLOSURE

That the injection of epinephrine hydrochloride (1:1000 solution) and the ingestion of ephedrine preparations have a specific action on the conducting mechanism of the heart can no longer be doubted. These drugs may not only yield an increase in the basic ventricular rate during established auriculoventricular dissociation, but can also stimulate the auriculoventricular pacemaker to function in the presence of widespread disease of the node. These drugs must necessarily so sensitize the auriculoventricular conduction mechanism, that even though impairment to the circulation is very definite, the threshold of impulse passage is heightened and because of this, in many instances, it is possible to restore normal sinus rhythm by their use, even though it be for only short intervals at a time. Consequently, despite the presence of coronary artery involvement with infarction of the heart, epinephrine hydrochloride is the drug of choice in patients in whom symptoms arise as a result of impaired circulation to the auriculoventricular node and consequent interference with impulse passage and impulse formation.

Indeed, I feel that without epinephrine injections at a time when stoppage of the ventricles takes place, many patients would succumb to the anoxemia and resulting cerebral trauma in the wake of repeated

syncopal attacks. Each patient, however, must be studied individually and the drugs and their dosages must be so adjusted that no lasting systemic manifestations result from their administration.

As a rule, it is expedient to tide over a patient when he is having his syncopal attacks with repeated intramuscular injections of epinephrine hydrochloride in doses of 1 c.c. of the 1:1000 solution, either until normal rhythm is restored or until the basic level of the heart, during auriculoventricular dissociation, remains fairly fixed, that is, when it does not vary more than five beats per minute. With this basic level relatively stationary, ephedrine sulphate in 30 mg. doses may be substituted orally for the epinephrine. This dose may then be repeated three or four times a day depending on the tolerance of the patient for the drug. The main complaints following its excessive use or due to the unusual susceptibility of a patient to it are profuse sweating, marked bodily tremors, and occasionally diarrhea, all of these signs being transitory. Eventually, most patients learn the exact amount which is sufficient to keep their heart rates and rhythms relatively fixed and yet not enough to cause systemic manifestations.

Definite proof that the ephedrine is essential to the maintenance of a sensitized pacemaker is the fact that its repeated withdrawal in patients with fresh disease of the circulation to the auriculoventricular node has invariably resulted in a diminution of the ventricular rate, with the appearance of syncopal attacks.

There is only one contraindication to the use of these drugs that I have encountered in patients with myocardial infarction, auriculoventricular dissociation, and recurrent syncopal attacks. It is in patients with the chronic phases of arterial closure to the node in whom the syncopal attacks are the result of transient periods of ventricular fibrillation and not of standstill of the ventricles.²⁷ Since similar observations have not as yet been reported in the acute phases of coronary artery closure, there is hardly any likelihood of precipitating ventricular fibrillation with ephedrine sulphate when the ventricles are at a standstill.

Of atropine sulphate, another drug that has been used to stimulate the auriculoventricular pacemaker, there is little to be said. In two patients of this series the injection of atropine sulphate in the early stages of the block was followed by transitory increase in the basic ventricular rate. It must be assumed that the extrinsic nervous mechanism of the heart has an influence over the auriculoventricular node in some patients. Atropine sulphate, however, is used primarily for the pulmonary edema that accompanies a coronary artery lesion frequently, and I have seen only good results following its repeated use for this purpose. In doses of 1/75 of a grain, injected intramuscularly, a lung inundated with edema may be cleared in half an hour.

SUMMARY

1. A study was made of fifteen patients exhibiting the Adams-Stokes syndrome following an acute coronary vessel closure. This group formed one-third of a series of forty-five patients with the Adams-Stokes syndrome seen during a period of four years. There were thirteen males and two females, the youngest being fifty-three years of age and the oldest seventy-one years. In each instance there was evidence of antecedent hypertension, and six patients showed signs of congestive heart failure prior to the present symptoms.

2. Of the fifteen patients, four died within an average of four days, the rhythm returning to normal in two. Seven lived for an average of twenty-six months, with either transient or complete auriculoventricular dissociation alternating during that time. Four are still living with normal sinus rhythm.

3. A permanent drop in the blood pressure after the establishment of a basic rhythm following the acute coronary vessel closure was the most persistent sign of the presence of that lesion.

4. The immediate treatment of such patients consists in the application of warmth to the body to overcome the initial shock and the repeated intramuscular injections of epinephrine hydrochloride until the block is either lifted with a return of normal sinus rhythm, or else a relatively fixed basic ventricular rhythm is established in the presence of auriculoventricular dissociation.

5. The after-care of those patients who still show auriculoventricular dissociation must include the daily administration of ephedrine sulphate to prevent a slowing of the basic ventricular rate. According to the results obtained, neither of these drugs is contraindicated in patients with acute coronary vessel closure in whom the circulation to the auriculoventricular node is involved.

6. Since the auriculoventricular node is in the upper part of the interventricular septum and is supplied by an arterial system in the posterior part of the heart, it may be concluded that patients with complete heart-block and Adams-Stokes syndrome as a result of an acute coronary vessel closure have an infarct in the posterior wall of the left ventricle and the adjacent septum.

7. The electrocardiographic pattern of infarction of the ventricle does not hold true for patients with auriculoventricular dissociation, for, in most of our instances, the electrocardiogram showed intraventricular conduction disturbance.

8. Since, of the fifteen patients with complete heart-block and Adams-Stokes syndrome who survived the acute coronary vessel closure, seven lived an average of twenty-six months; it appears that the prognosis for such patients, as far as longevity is concerned, is not bad.

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COARCTATION OF THE AORTA (ADULT TYPE)

CLINICAL AND EXPERIMENTAL STUDIES*

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COARCTATION of the aorta is a stricture or stenosis of the aorta. This narrowing is usually found at, or just proximal to, the junction with the ductus arteriosus. Two types, the infantile and the adult varieties as described by Bonnet,¹ are generally recognized. The infantile type, most frequently seen in the newborn, is a diffuse narrowing, or a complete absence of the isthmus (that part of the aorta between the left subclavian artery and the junction with the ductus Botalli). This form is commonly associated with other congenital anomalies and is not compatible with adult life. Infantile coarctation is believed to develop before birth. Adult coarctation is a constriction or obliteration of the aorta at or near the junction of the ductus Botalli with the aorta. Skoda² suggested that in the adult type a portion of the tissue peculiar to the ductus extends into the adjacent aortic wall, and, as the atrophy of this tissue occurs, it results in constriction or occlusion of the aorta. The process is a comparatively slow postnatal development and adequate collateral circulation has time to become established. Complete descriptions of the pathology and theories of pathogenesis are available in the papers of Abbott³⁻⁷ and of Blackford.⁸

The symptomatology in coarctation of the aorta varies a great deal. Abbott⁶ placed patients in three groups:

1. Those in whom symptoms are absent.
2. Those in whom symptoms are late in developing. These symptoms are flushing of the face, profuse sweating in upper portion of the body, headaches, tinnitus and dizziness, all of which can be associated with the hypertension in the upper extremities, head and neck. At the same time or independently, circulatory insufficiency and intermittent claudication of the lower extremities are often present. In this group sudden rupture of the heart, aorta, or vertebral arteries occurs.
3. Those in whom symptoms are present throughout life. These are usually the symptoms of myocardial failure which often result from secondary chronic valvular disease.

In contrast to these inconstant subjective features of coarctation of the aorta, the physical signs are diagnostic in all the cases prior to terminal complications, as will be discussed below.

CASE REPORT

A nineteen-year-old boy of Austrian parentage entered the medical clinic of the New York Post-Graduate Hospital with a slip of paper detailing the following complaints and symptoms: self-consciousness, nervousness, dreaming every night, tense-

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ness, inability to relax in public, redness of face, especially of the nose, when cold, sweating of hands and armpits, small size of the right side of the chest and arm.

The family history was negative. The patient's two brothers and two sisters were well and free from all physical defects on routine examinations at school. The patient had had the usual childhood diseases. His tonsils were removed at the age of two. His mother stated that he had had rheumatic fever at three. He attended school when six years old and has not been acutely ill since. Another tonsillectomy was performed at ten years of age. When eleven years old he ran a 40-yard race. As a rule he was considered a speedy runner, but on this occasion he was not conscious of the racing interval; at the finish he seemed to awaken and was surprised that he had not won. During moments of excitement, as in fighting, the patient states that his mind would go blank. He remained active in athletics, with no signs or symptoms of cardiac embarrassment, until six years ago when he was told at school that he had heart trouble and high blood pressure. Since then, on the advice of a physician, he has partially curtailed his activities. The patient complained of having been troubled by dreams all his life, and it seemed to him as though his mind was never at rest. He had always been self-conscious and had

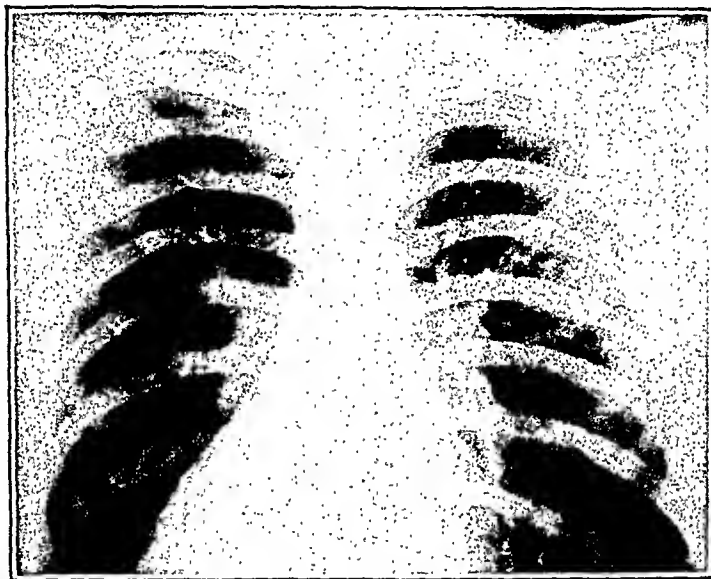


Fig. 1.—X-ray plate of chest showing left-sided hypertrophy of heart, dilatation of the ascending aorta, absence of the aortic knob, and notchings of the inferior border of the ribs.

complained of flushing of his face for eight or nine years. This appeared to be increasing lately. His hands were always clammy, and for the past two or three years his feet have been cold. His nose bled at the slightest trauma.

Physical examination revealed the following: The patient was unusually well-developed, and, although he did not seem nervous, his cheeks were flushed and perspiration trickled from his axillae. His pupils reacted normally to light and accommodation. The arteries of the fundi appeared threadlike, showed a slight degree of tortuosity and streaking, and angiospasm was indicated further by the obliteration of the lumen in the left temporal branch. The veins appeared full. Carotid pulsations in the neck were plainly visible as was also a pulsation at the suprasternal notch. The upper border of a vessel running transversely at the suprasternal notch pulsated strongly. The thyroid gland was not palpable. The precordium appeared to bulge. Expansion was equal and free, and Litten's phenomenon was present, indicating that the diaphragm was not adherent. The lateral thoracic arteries were seen pulsating on both sides, and in a strong oblique light intercostal pulsations were to be observed in the posterior axillary line. The intercostal pulsations and those about the scapulae were readily felt with the finger tips.

A systolic murmur was heard over these vessels. The apex impulse was 10 cm. to the left of the median line in the fifth intercostal space and was distinctly heaving. A loud, rough systolic murmur was heard at the aortic area and was transmitted upward into the neck and through to the back. There was a blowing systolic murmur at the mitral area. The pulse rate was 90 and the rhythm regular. The fingers were blunt but no clubbing was evident. The hands were clammy. Brachial and radial pulsations were marked; femoral pulsations were low and flattened. Pulsations could not be felt in the popliteal, posterior tibial, and dorsalis pedis arteries. The feet were warm. The blood pressure in both arms was equal and ranged from 238/128 on the patient's first visit to 178/90 on subsequent occasions. The popliteal blood pressure was 96/72 at the time of the latter brachial reading, but no popliteal readings could be obtained subsequently upon repeated attempts.

Laboratory Findings.—Blood count showed hemoglobin, 100 per cent; red blood cells, 5,020,000; white blood cells, 8,900. Differential—polymorphonuclears, 64 per cent; lymphocytes, 36 per cent.

Urinalysis showed no abnormal findings. A Wassermann test was negative.

X-ray examination (Fig. 1) showed erosions of lower borders of ribs posteriorly. Increase in total heart area, with transverse diameter 1 cm. above the average normal. The aortic arch appeared reeded; the transverse and the descending arch of the aorta could not be found.

Basal metabolic rate was 11 per cent above the average normal.

Renal function tests showed blood urea nitrogen, 10.9 mg. per 100 c.c.; blood nonprotein nitrogen, 27.2 mg. per 100 c.c.; urea ratio, 40 per cent; urea clearance, 106.6 per cent of normal.

Vascular studies are reported and interpreted below.

DISCUSSION

Although there may have been rheumatic fever at three years of age, it is possible that the murmur resulting from the congenital anomaly prompted this diagnosis. While the patient was at school, his condition was not recognized and in a clinic he was told that he was a psychoneurotic. The brachial hypertension in a nineteen-year-old subject with a loud systolic murmur at the base of the heart suggested the existence of coarctation of the aorta. The diminished circulation in the lower extremities and the collateral circulation visible on the chest wall established the diagnosis.

Normal renal function, as indicated by the urea ratio²² and the urea clearance test,²³ is evidence of adequate circulation throughout the body and to the kidneys.

Since most of the symptoms were referable to increased arterial pressure in the upper part of the body, the effect upon the activity of the thyroid gland was of interest. The basal metabolic rate proved to be normal.

The following studies of the peripheral circulation were done in the vascular clinic under the supervision of Dr. Irving S. Wright.

The surface temperature over the entire body of our patient was within normal limits. On the trunk there was no change indicating a level at which the peripheral circulation was diminished, whereas the extremities showed the normal downward temperature gradient toward the periphery. The temperature of the upper extremities was not con-

sistently higher than that of the lower extremities, despite the difference of blood pressure and major vessel activity. An interesting finding was the definitely higher temperature of the right leg as compared with the left.

The oscillometric curves (Fig. 2) were unusual but were anticipated, in that the curves of the upper extremities showed a much greater oscillometric swing than those of the lower extremities. The curves of the left leg were definitely greater than those of the right leg. This did not correspond with the surface temperature readings as noted above.

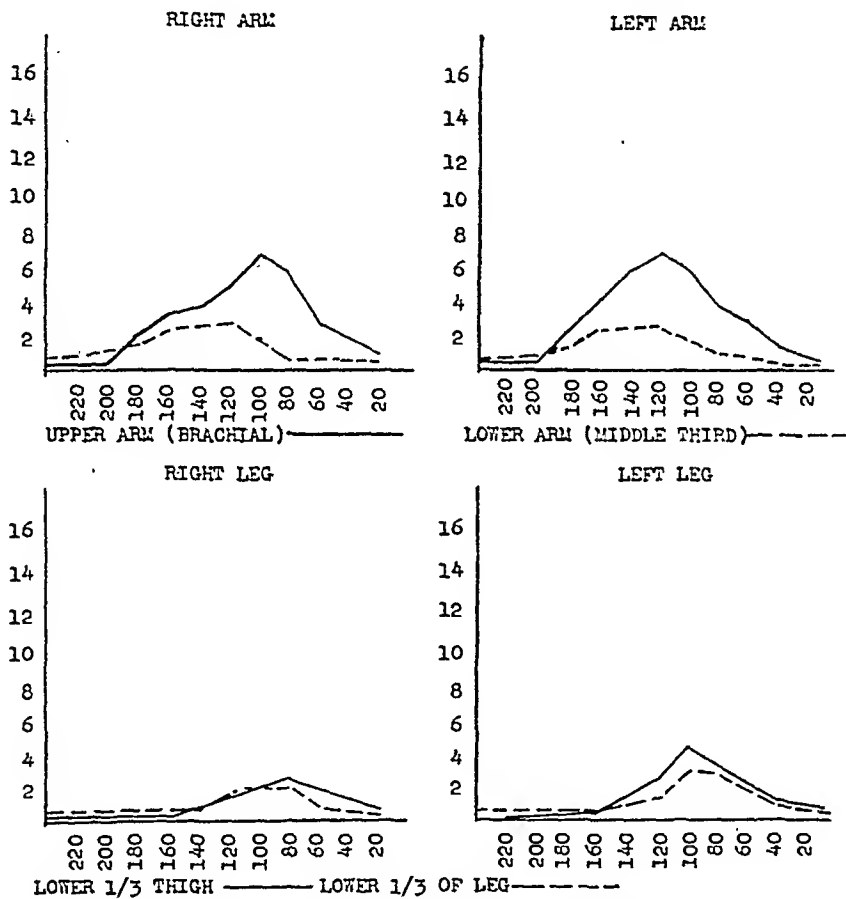


Fig. 2.—Showing oscillometric curves of the upper extremities to be much greater than those of the lower extremities.

A series of hot water immersion tests was performed, according to the technic of Gibbon and Landis.²⁴ Figures 3, 4, 5 and 6 show that it was possible to produce elevation of the surface temperature of the unimmersed extremities to within normal limits by a variety of combinations of immersed extremities. Figure 7 shows the curve of intravenous temperature of the left antecubital vein, as compared with the surface temperature of the finger tips of the right and left hands, following immersion of the feet in hot water. The intravenous temperature changes accompanied but did not precede the surface temperature changes. The significance of this finding is a moot question at present.

The nail fold capillaries at the finger tips were tortuous, normal in the number active, dilated, and rather bizarre in form. The rate of flow

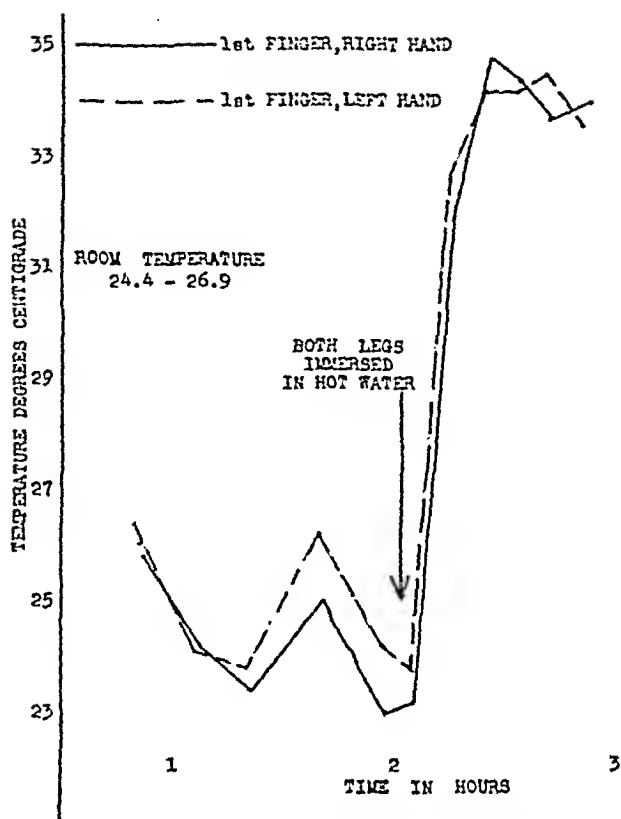


Fig. 3.

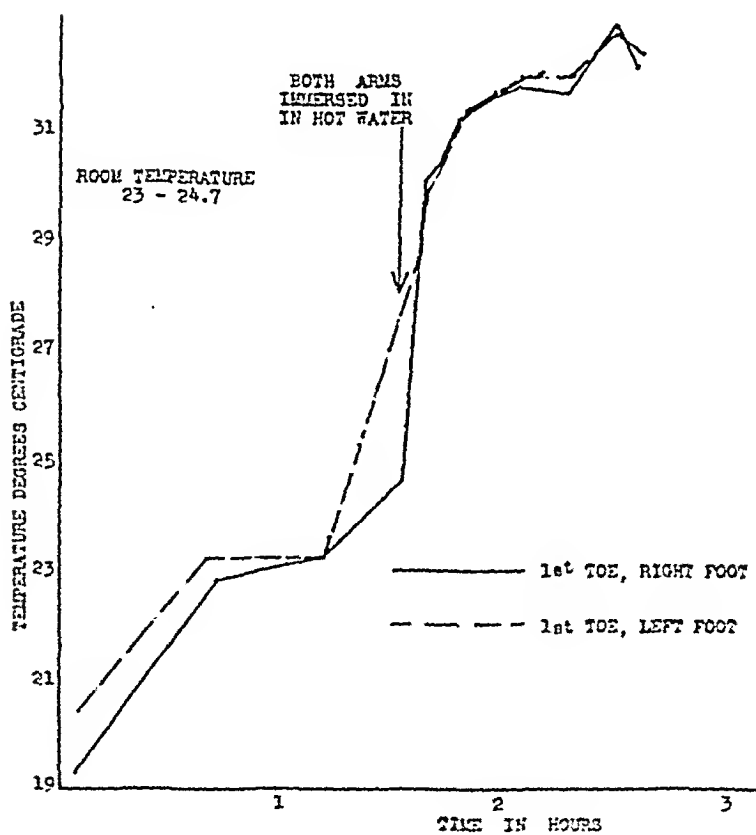


Fig. 4.

varied rapidly from fast to slow. The capillaries at the nail folds of the toes were diminished in number, small, constricted, with a slow flow, and were difficult to visualize.

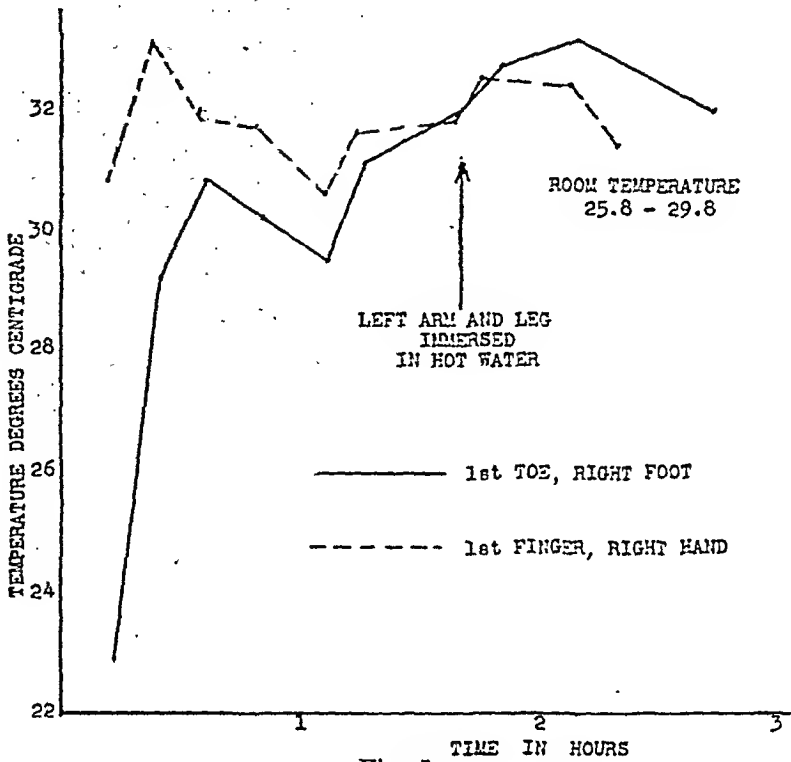


Fig. 5.

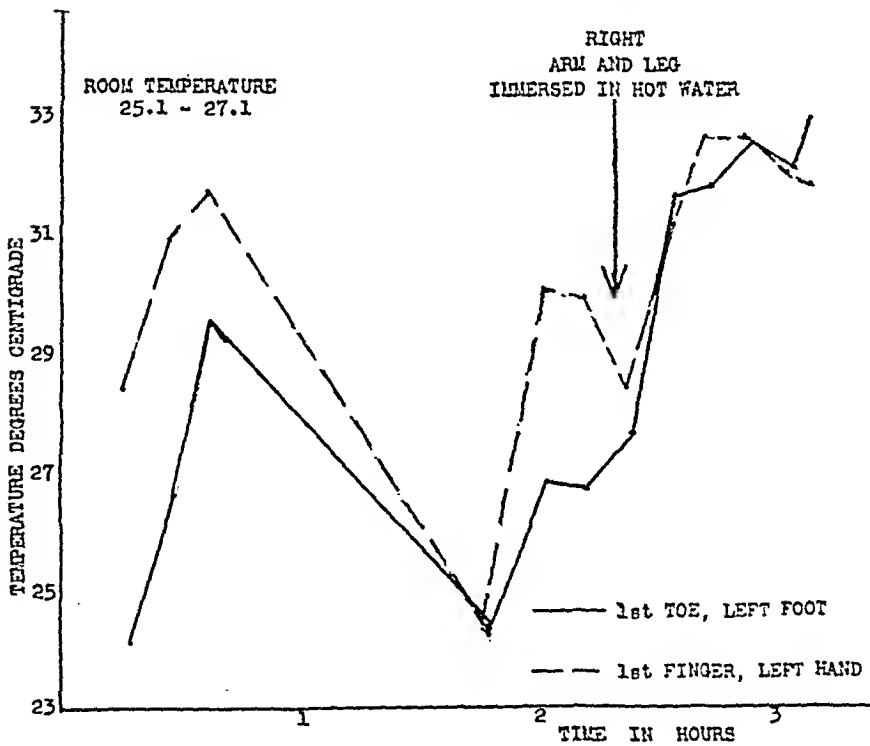


Fig. 6.

The studies of the peripheral circulation demonstrated the remarkable compensatory circulation supplied by the collateral arteries, which permitted normal vasodilatation, as measured by surface temperature readings.

Most cases of coarctation of the aorta remain undiagnosed during life. Abbott⁷ reported autopsy findings in 200 cases, 86 per cent of which were overlooked clinically. Blackford⁸ found from necropsy reports of approximately 68,300 routine cases, that the incidence of coarctation was about one in 1,550. Paris⁹ described the typical pathological findings as early as 1791. Meekel¹⁰ (1827) first observed erosions of the ribs, but his illustration shows these lesions on the superior costal border, while the predominant lesions as generally reported are found on the inferior border of the posterior portion of the ribs. Legrand¹¹ (1835) made a diagnosis of obstruction of the thoracic aorta based on evidence of col-

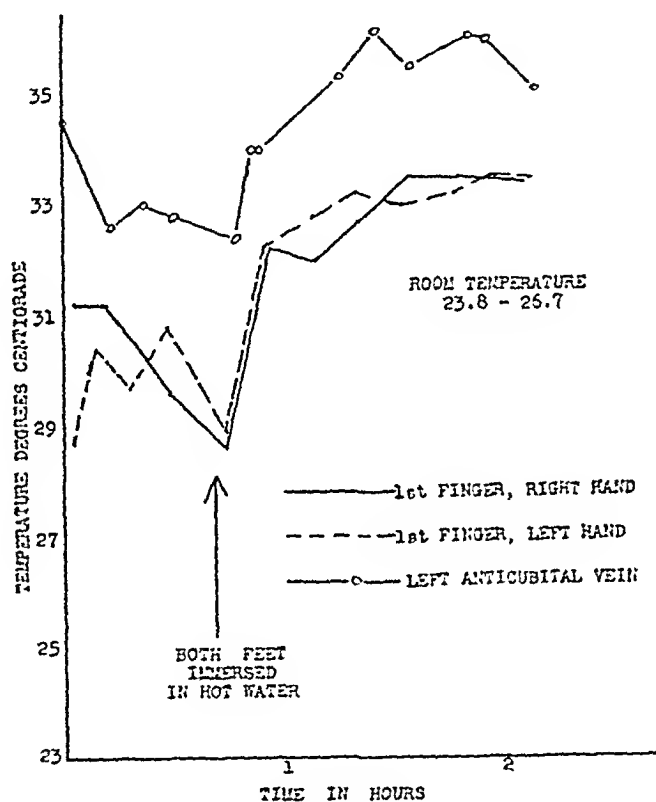


Fig. 7.

lateral circulation over the chest with a diminished femoral pulse. The actual diagnosis of stenosis of the aorta at the ductus was first made in 1848 by Oppolzer, according to Hamernjk.¹² Potain¹³ demonstrated hypertension in the upper portion of the body in 1892. Abbott,^{3, 4, 5} in 1908 and 1915, called attention to the clinical aspects of coarctation of the aorta and in 1927 supplemented these papers. King¹⁴ (1926) emphasized the important clinical features of stenosis of the aortic isthmus and noted that while only one case was discovered at Johns Hopkins Hospital from 1889 to 1923, three cases were diagnosed in the next three years. In 1928 Abbott and Hamilton⁷ made a further extensive report, as did Blackford.⁸

Over one hundred years after Meckel had observed costal erosions as a post-mortem finding, the information was applied clinically by Railsback and Dock¹⁵ (1929). They called attention to the roentgenographic findings of scalloping of the inferior borders of the ribs, absence of the aortic knob, dilatation of the ascending aorta, defect in the aortic arch and left ventricular hypertrophy. Abbott and Hamilton,⁷ one year before (1928), had published a roentgenogram showing costal erosions but had failed to comment upon it.

Scheele¹⁶ (1870) made simultaneous tracings of the radial and femoral pulsations. His records show the femoral pulse rising more slowly than the radial, but, according to Lewis,¹⁷ this delay in Scheele's tracing is not measurable. Laubry and Marre¹⁸ (1916) recorded the slow rise of the femoral pulse but observed no delay in the upstroke. Railsback and Dock¹⁵ (1929), by simultaneous electrocardiograms and optical pulse measurements, found the femoral to occur 0.025 sec. after the radial. Blumgart and his associates¹⁹ (1931) stated that normally the femoral pulsation should precede the radial 0.01 to 0.02 sec., but in two cases of coarctation they found the femoral followed the radial by 0.15 sec. and 0.05 sec. Dock²⁰ (1932) called attention to the difference in quality and time of the radial and femoral pulsation as an easy and reliable diagnostic test. Lewis¹⁷ (1933), investigating six cases of coarctation and five normal subjects, measured the optical pulse and the electrocardiogram simultaneously. He found that normally the femoral upstroke precedes the radial by 0.01 sec., while in coarctation femoral upstroke follows the radial by 0.03 sec.; this delay, he says, is of little clinical significance; however, he finds the lag of the summit of the femoral pulsation is 0.145 sec., and this is easily appreciated with the unaided fingers. Leaman,²¹ in the same year, called attention to the diagnostic value of the palpation for a low femoral pulsation in coarctation. Lewis (1933) discussed the subject of aortic coarctation and presented nine cases. Thus each year, as the diagnostic features of this condition have been emphasized and elaborated, there has been a steady increase in the recognition of these cases. In 1934 the *Quarterly Cumulative Index* contained reference to twenty papers dealing with this subject.

The prognosis in this condition is difficult to determine for an individual case but in general may be based upon the compilations of Abbott. Abbott⁵ found the average age at death to be thirty-two years, with a range from three years to ninety-two years. The cause of death was as follows: congestive heart failure, 60; sudden heart rupture, 2; rupture of the aorta, 38; cerebral complications, 26; bacterial endarteritis, 14. Although most of Abbott's patients died of cardiac insufficiency, Lewis¹⁷ points out that cases of coarctation are the best evidence that prolonged overwork of the heart in itself does not cause myocardial failure. He observed patients in whom the heart continued

to beat for as long as sixteen years against a systolic pressure of 200 and a diastolic of 100. He states that only 25 per cent of the deaths in coarctation are attributable to congestive heart failure, and in those cases infectious diseases or changes due to advancing age are responsible for the sudden incompetence of the heart. The important fact, as Lewis sees it, is that failure is not inevitable.

SUMMARY

A case of coarctation of the aorta, of the adult type, is reported, together with renal function tests, studies of surface temperature, oscillographic determinations, and capillary studies.

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THE NONFILAMENT LEUCOCYTE COUNT AFTER CORONARY ARTERY OCCLUSION*

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ALTHOUGH when acute coronary occlusion can be recognized clinically the prognosis is serious, it is known that the majority survive the acute attack. The clinical findings that would suggest a less favorable outcome, according to White,¹ are "advanced age, a state of shock, an abrupt and pronounced fall in blood pressure, the prolongation of the severe substernal pain for more than two or three hours, the duration of fever for more than a few days, the presence of high fever (103 to 104° F.), a high leucocytosis—especially if maintained for a week or more, rapid and marked dilatation, gallop rhythm, ventricular paroxysmal tachycardia, heart-block, pulsus alternans, cardiac asthma, congestive failure, and embolic phenomena." The electrocardiogram generally gives confirmatory evidence of the presence of myocardial infarction, although it cannot be relied upon to inform us as to the extent and severity of this pathological change. Certain blood studies have been carried out in the hope of yielding useful information on this point. Knowing that absorption from necrotic processes causes lowering of the red cell sedimentation time, Rabinowitz and his coworkers² became interested in this reaction following acute coronary occlusion. In 10 such cases they found uniformly an increase in the rate, the change being most marked on the third to fifth day, and persisting longer than fever or leucocytosis. Burak³ reports a similar study on six patients. Steinberg^{4, 5} followed the nonprotein nitrogen level of the blood in cases after coronary occlusion and reported that a filtrate nitrogen, remaining high or continuing to rise, was of serious significance.

Many previous articles have mentioned the characteristic increase in the total leucocyte count. White¹ states that the grade and duration of leucocytosis is a useful clue to the size of the infarct and hence to the prognosis. Libman and Sacks⁶ state that leucocytosis is the most frequent significant feature of the condition. Of a series of 74 patients reported by Levine,⁷ only 4 had a total white blood cell count of less than 10,000. All of the 14 patients reported by Coffen and Rush⁸ had leucocytosis after acute coronary occlusion, and all but 3 of the 19 reported by Wearn.⁹ Hamman¹⁰ states that the average leucocyte count in this condition is 12,000 to 15,000. Rarely is the count more than 30,000. Levine and Brown¹¹ had one such patient with a 34,500 count, and Hines¹² had one in which the total count exceeded 100,000 for a

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period of twelve days. In our own entire series of coronary occlusion cases 35,700 has been the maximum count. This patient died, and autopsy showed extensive infarction of the myocardium. It is usually assumed that such marked increases in the total white cell count indicate extensive acute myocardial pathological change, and therefore a more serious prognosis, and in the main this is borne out by the outcome in such cases.

In applying the filament-nonfilament count in several patients after coronary occlusion, we were struck with the fact that there was a "left shift" present which was frequently quite pronounced. It was then decided to follow several such consecutive cases, doing frequent simul-

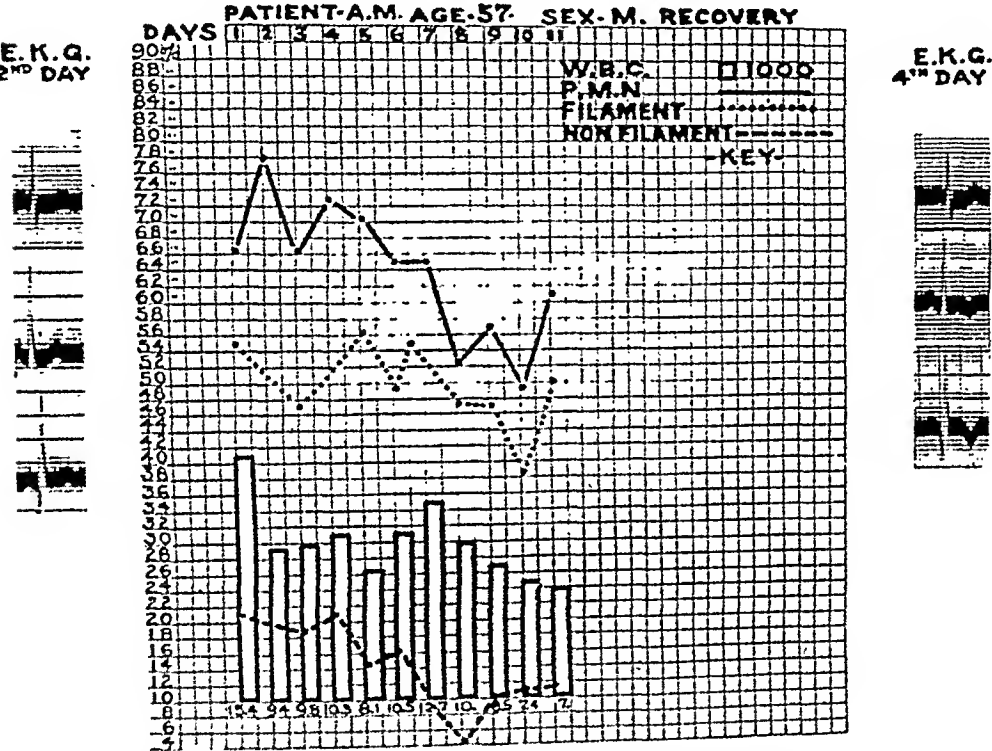


Fig. 1.—An example of a rather mild and favorable case of coronary thrombosis. The electrocardiograms are offered corroborating the diagnosis. The nonfilament percentage curve is relatively low and a wide separation is seen between it and the filamented cell curve.

taneous total leucocyte counts and differential counts according to the usual type, as well as filament-nonfilament counts, plotting the results graphically. This procedure was carried out in fifteen cases of coronary artery occlusion, and a total of 189 such counts were made. The differential percentages were obtained by counting 200 cells on each slide. The counts and slides were usually obtained between 9:00 and 11:00 A.M., and only from hospitalized patients. Curves were plotted for the individual patients, and subsequently, composite graphs were made of the eleven who recovered and the four who died. In these charts are shown the total leucocyte count, the polymorphonuclear neutrophile percentage,

the filament and nonfilament counts and, in one of the combined graphs, the eosinophile percentages as well. It was hoped that in following these counts serially some information might be encountered which could assist the accuracy of prognosis in the acute attack of coronary thrombosis. It is realized that comparing averages of a series of four fatal cases to those obtained from a series of eleven recovered cases is open to some criticism. However, as in any series of acute coronary occlusion, the nonfatal cases will exceed the fatal ones during the first several weeks; such a disproportion will always be found if the cases are consecutive.

THE TOTAL LEUCOCYTE COUNT

In both the recovered and fatal cases, the total white cell count was highest on the second and third day after occlusion, averaging about

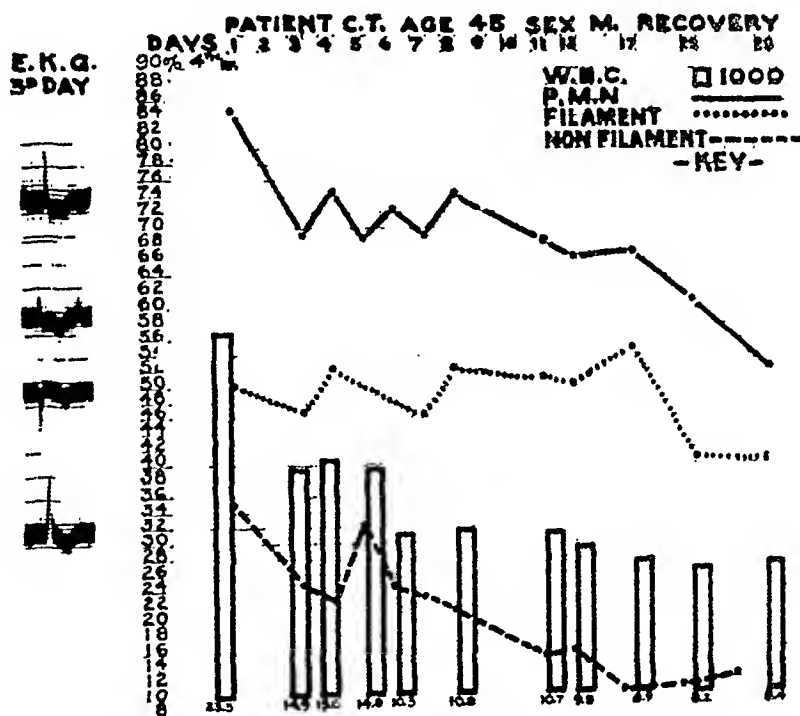


Fig. 2.—Another patient with a favorable prognosis. Progressive drop of the non-filament count after the fifth day. Wide separation between the filament and non-filament curves. Electrocardiogram taken on third day shows characteristic changes of coronary occlusion.

2,000 higher in those patients who died. It was 17,700 in the fatal, 15,900 in the recovered group. A slight increase was maintained throughout in the four fatal cases. It may also be noted that an average leucocytosis of about 10,000 continued, even in the recovered cases, to as late as the nineteenth day.

THE POLYMORPHONUCLEAR PERCENTAGE

This percentage was at its maximum during the first few days, and thereafter it fell progressively in both groups. After the eighth day in the recovered group it continued to fall slightly, whereas in those patients who died it remained above 70 per cent.

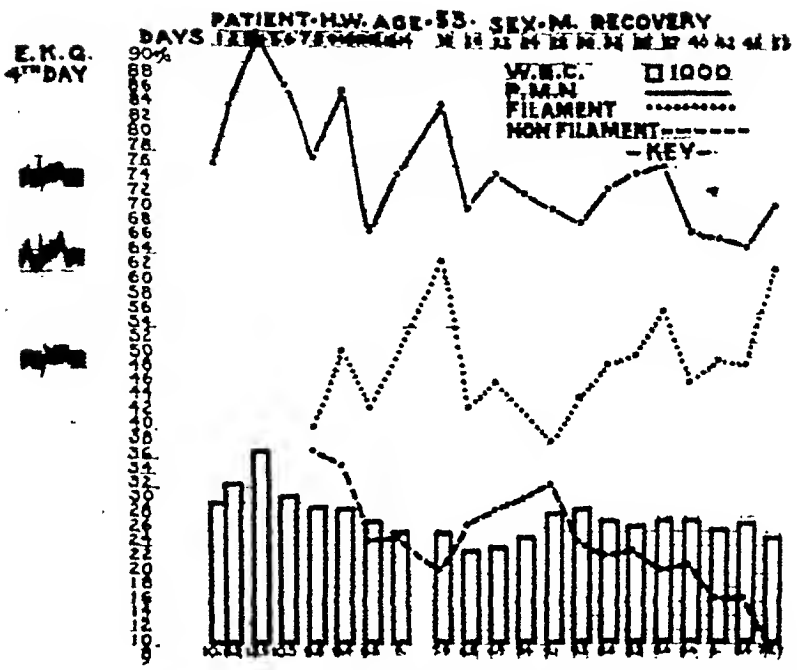


Fig. 3.—A patient who recovered in spite of a severe coronary obstruction. Unfortunately the nonfilament counts were not begun until the eighth day. Nonfilament percentage curve and filament curve are almost together on eighth day, and the nonfilament curve rises to a secondary peak of 32 per cent on the twenty-eighth day and afterward falls progressively to normal on the fifty-third day. Characteristic electrocardiogram on fourth day.

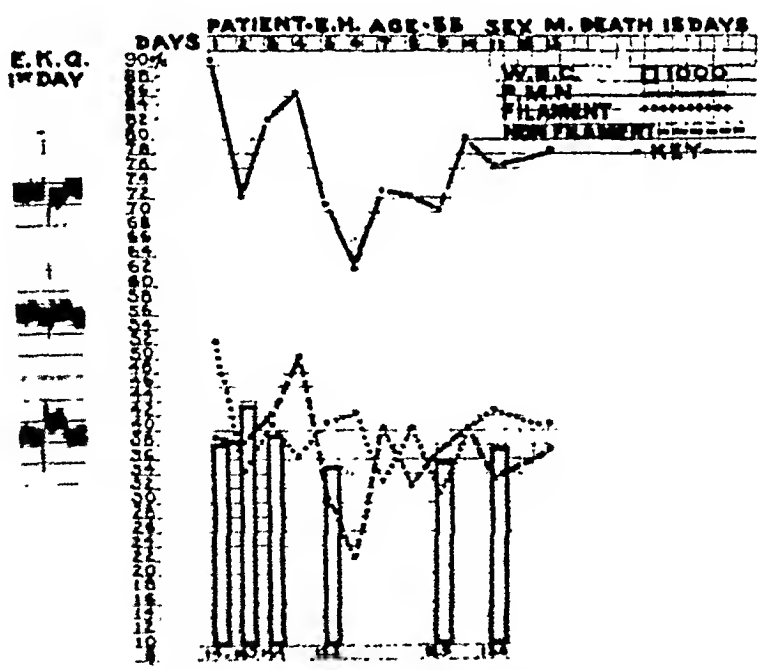


Fig. 4.—Fatal case with death on fifteenth day. Note relatively high initial polymorphonuclear count and peak of nonfilamented percentage as high as 50 per cent on the fourth day. The filament curve repeatedly crosses the nonfilament curve after the fourth day. Typical electrocardiogram.

THE NONFILAMENT COUNT

The neutrophilic leucocytes were recorded as nonfilamented and filamented cells. Farley, St. Clair, and Reisinger¹³ suggested this simplification. Their average percentage of one lobed cells in ten normal persons was 9.2 per cent, with 16 per cent stated to be the upper limit of normal. Needles¹⁴ in an equal series obtained 8.45 per cent as the average normal and used 16 per cent as the upper limit of normal. Schilling¹⁵ with normal total white blood cell limits at 5,000 to 8,000 reports 3 to 6 per cent as the normal number of nonfilamented cells.

In our fifteen patients followed in this manner, the nonfilament or one lobed cells were uniformly elevated above the upper limit of normal (16 per cent). It was noted in averaging the recovered and fatal cases that this count offered a more striking contrast than was presented by either the total white cell count or the polymorphonuclear percentage. In both the recovered and fatal group, the count commenced relatively high on the first day after occlusion and had a rather sharp drop the second day, rising again to a maximum on the fourth day. In the recovering patients, after the eighth day it fell gradually to a normal level on the sixteenth day. In the four patients who died, the average nonfilament percentage was almost double that in the recovering patients and, after the eighth day, instead of declining, the curve steadily rose as high as 37 per cent on the twelfth day. This nonfilament count in the early stage of infarction was often proportional to the total white cell count, except for the sharp drop on the second day. Later on, however, in the recovered group it fell to normal even when the total white cell count remained around 10,000.

EOSINOPHILE PERCENTAGE

In certain acute infections, the reappearance of eosinophiles and their increasing percentage are thought to be some of the earlier evidences of subsidence of the infection and the onset of recovery. A moderately striking contrast is offered in the comparison of the average eosinophile percentage curve of the fatal to that of the recovering patients after coronary occlusion. In the fatal group, no eosinophiles were found before the fifth day after occlusion. The curve then rose gradually to a maximum of 1.7 per cent eosinophiles on the tenth day and dropped abruptly thereafter to zero on the twelfth day. In the recovering patients, a 0.4 per cent eosinophile average was present the first day after occlusion, and the curve increased progressively up to 3.6 per cent on the fifteenth day.

THE FILAMENT COUNT

Nothing has been said up to this point regarding the graph of the filamented neutrophiles since after all this percentage is complementary to the nonfilamented curve and simply indicates the proportion of more

mature neutrophils to the total leucocyte count. However, a review of all our fifteen individual cases, as well as of the combined graphs, reveals some points of interest. First, in three out of the four fatal cases the nonfilament curve crossed the filamented graph or was repeatedly intermingled with it, and in each of the three charts intersection of these curves occurred as late as the sixth day and after. Of the eleven recovered cases the filament and nonfilament curves intersected in three cases on the fourth day and in one on the fifth. After this day, a wide separation of the two curves was present in all the recovering patients. Similarly, a comparison of the combination graphs of the patients who died and those who recovered reveals that in the fatal group the filament and nonfilament curves are separated by a relatively

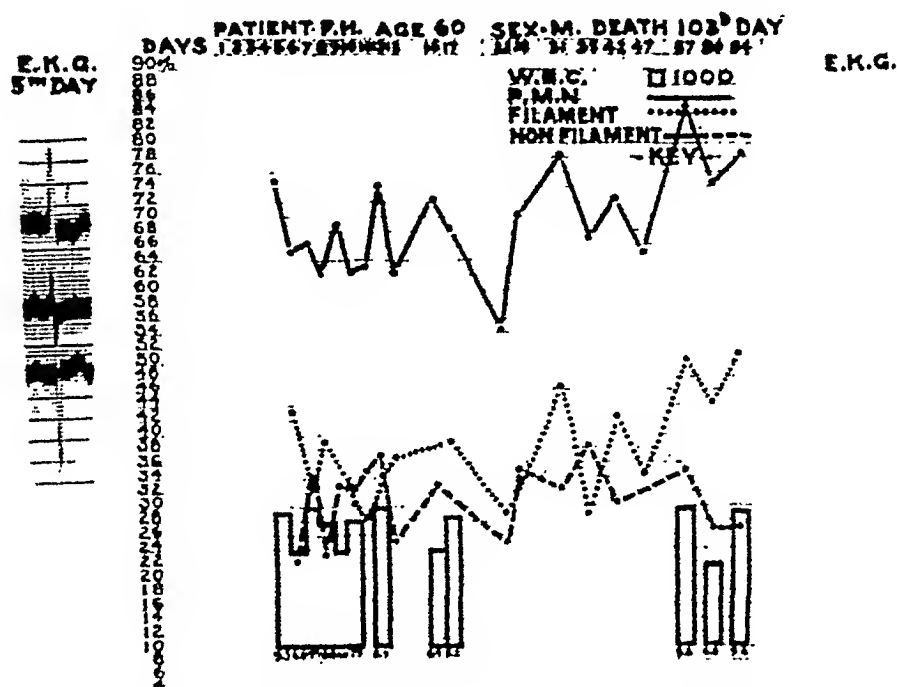


Fig. 5.—Fatal case with death on 103rd day. Prognosis seemed unfavorable during observation. Note nonfilament curve persisting above 30 per cent and repeatedly intersecting the filament curve after the fifth day.

slight space, are quite close together on the fourth day, and meet on the seventh and eleventh days. The "recovered" group averages, however, maintain a wide separation between the filament and nonfilament percentage curves throughout a nineteen day period.

Many conditions other than infections produce leucocytosis, such as the taking of food, exercise, and pregnancy. Walton¹⁶ reports a consistent elevation accompanying fractures. Pepper¹⁷ cites cerebral hemorrhage with 16,600 leucocytes and paroxysmal tachycardia with 17,100. Patients with congestive cardiac failure usually show a slight leucocytosis.

The peculiar conformation of the nonfilament curve in both the recovered and fatal cases in the first four days after acute coronary oc-

clusion—showing a high figure the first day, a sharp drop the second, followed by a progressive rise to a maximum on the fourth day—would suggest a need for explanation. Libman and Sacks⁶ report leucocytosis

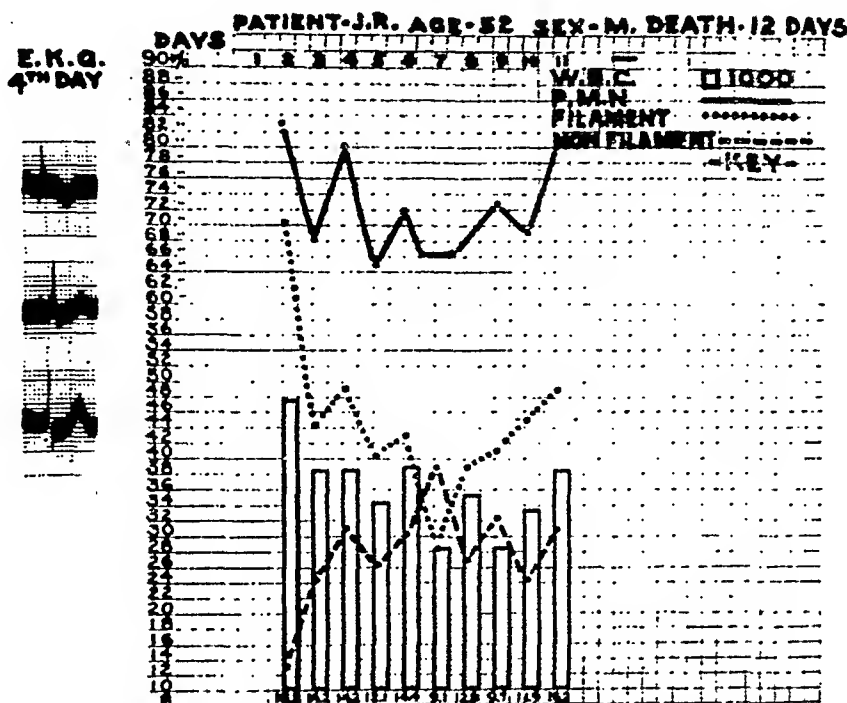


Fig. 6.—Fatal case. After the fourth day the nonfilament curve remains above 30 per cent and is intersected by the filament curve on the seventh day. Characteristic electrocardiographic changes.

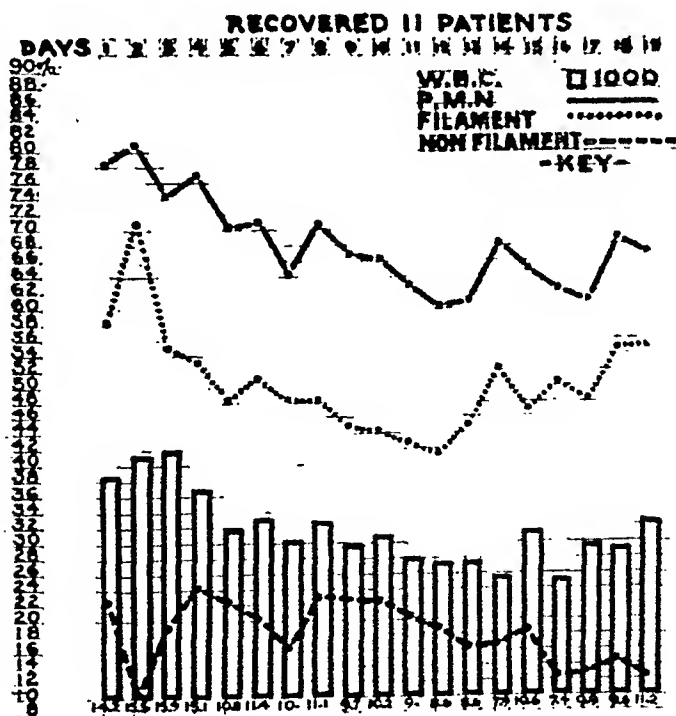


Fig. 7.—Graph showing average counts on the eleven patients who recovered. Note wide separation of filament and nonfilament curves. Moderate elevation of non-filamented percentage to 22 on first day and sharp drop to a normal level on second day, then progressive rise to maximum of 24 on fourth day with gradual decline afterward. The polymorphonuclear percentage falls gradually from the first day.

occurring within one and one-half hours after acute coronary occlusion. Fraenkel and Hochstetter¹⁸ observed leucocytosis in partial asphyxiation of rabbits, the maximum being within five hours. Holst¹⁹ believes that the early leucocytosis in coronary occlusion is due to an excess of carbon dioxide. Reveno²⁰ notes 14 per cent nonfilamented leucocytes in congestive cardiac failure. Fanelli,²¹ likewise, found a usual but inconstant slight increase in the nonfilament percentage. He suggests this may be due to two factors: the increased carbon dioxide percentage stimulating the production of young forms and the lessened oxygen content preventing the usual maturation to older forms. The initial high nonfilament percentage in our series of patients may be due to shock

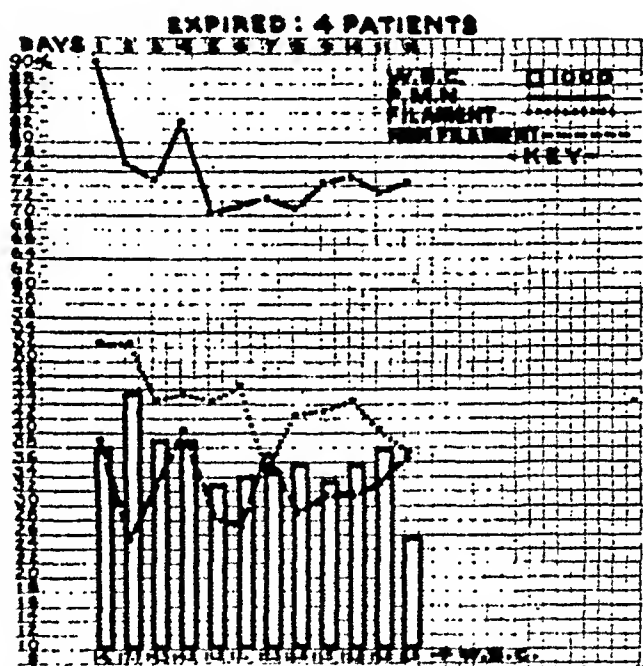


Fig. 8.—Graph showing average counts in four fatal cases. The polymorphonuclear percentage is higher than in Fig. 7. The nonfilament count persists at a high level, above 30 per cent intersecting the filament curve on the seventh day and again meeting it on the twelfth day. Note the nonfilament rise the first day to 38 per cent with a drop the second day to 24 per cent, the secondary peak of 40 per cent on the fourth day.

and excess carbon dioxide, while the sharp drop on the second day may be explained by a recession of this reaction and the absence at this point of the complete development of the myocardial infarction.

It is well known that after obstruction of arterial supply in any location, infarction takes time to develop and reach its maximum extent; furthermore, the speed of development is not always the same and may depend on many variable factors. Groyzel and his associates²² were not able to demonstrate any anatomical change in dogs earlier than ten hours after closing a coronary artery. Later on there developed edema, hemorrhage, and slight polymorphonuclear infiltration. When a myocardial infarct is large, it seems obvious that there will be a greater

opportunity for the absorption of toxic substances from the necrotic area, that a longer time will be required for repair and that a greater probability will exist for a fatal outcome during the early period after the coronary artery occlusion.

We believe that the curves encountered in the leucocyte and differential counts are directly related in the main to the evolution of the myocardial infarct. The combination of nonfilament count and eosinophile percentage behaves in this condition in the same way that it does in certain acute infections, i.e., early in either condition: when absorption from either infection or necrosis is marked, the nonfilament count is

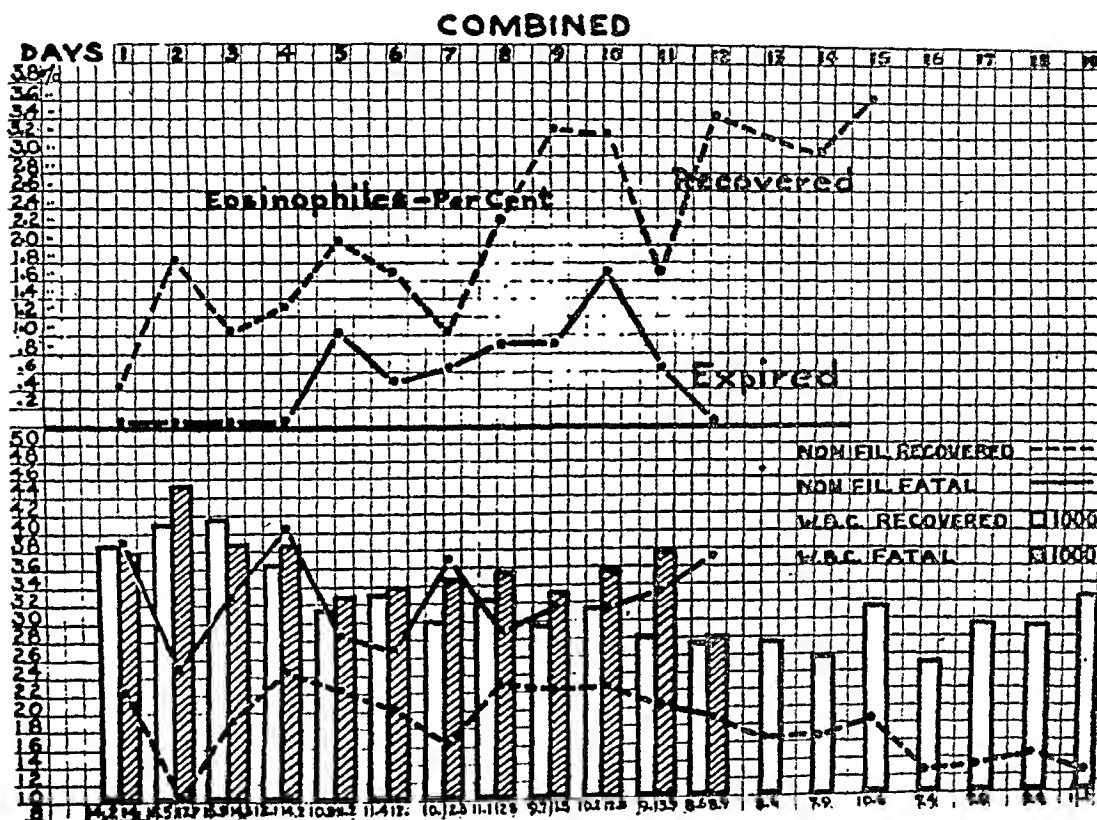


Fig. 9.—The upper half of this chart depicts the average eosinophile percentages in the recovered and fatal cases. Note the absence of eosinophiles in the fatal group before the fifth day, also the progressive upward trend in the recovering cases as high as 3.6 per cent on the fifteenth day. The lower chart compares the total leucocyte counts in the fatal and nonfatal cases, also the nonfilament percentage curves. The total white count maintains a slightly higher level in the fatal group. The nonfilament percentage is nearly twice as high in the fatal cases as in the recovered.

relatively high and the eosinophiles low or absent; while with the onset of recovery, the reverse is true, and the eosinophile curve rises as the nonfilament curve drops toward normal. In our cases, this change was most pronounced in the recovering or nonfatal cases about the eighth to tenth day.

SUMMARY

The total white cell count is increased after coronary artery occlusion, averaging from 13,000 to 18,000 in the first four days. In a fatal case

one count as high as 35,700 was encountered. The average leucocyte count has been found to be slightly higher in the patients who died than in those who recovered.

The polymorphonuclear neutrophile percentage is above normal, being somewhat higher in the fatal group than in the recovered group.

The average nonfilament curve was found to be almost twice as high in the fatal cases of coronary occlusion as in the recovering group, and in the combined graph of fatal cases the nonfilament average was as high as the filamented average on the seventh and eleventh days; while in the recovering group, although a few cases showed an intersection of these two curves on the fourth day, in the main there was a wide separation between them.

The eosinophiles were absent in the four fatal cases up to the fifth day, the curve slowly rising to 1.6 per cent on the tenth day, and then falling to zero on the twelfth day. The recovering group showed an earlier appearance of eosinophiles and a higher and more progressive rise to 3.6 per cent on the fifteenth day.

CONCLUSIONS

An unusually high total leucocyte count early after occlusion is thought to be of serious significance.

A nonfilament percentage curve persisting above 30 per cent beyond the fourth day after coronary occlusion would suggest a large area of infarction and hence an unfavorable prognosis.

An absence of eosinophiles or an eosinophile curve not rising above 1.5 per cent in the first ten days appears to be rather unfavorable.

A nonfilament percentage curve ranging below 25 per cent, and an eosinophile percentage appearing early and rising above 3 per cent would suggest a less extensive area of myocardial infarction and a greater probability of recovery.

The daily plotting of graphs of the differential and filament-nonfilament counts after acute coronary occlusion gives information of distinct value in estimating the prognosis and this information is superior to that obtainable from the total leucocyte count alone.

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AN ANALYSIS OF THE RELATIONS OF THE CORONARY CONSTRICTOR AND DILATOR NERVES IN THE CERVICAL VAGOSYMPATHETIC OF THE DOG* †

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COLUMBIA, MO.

THE original demonstration of coronary vasoconstriction was based on the effects of stimulating the cervical vagus (or vagosympathetic) in the cat. Upon stimulating this pathway Porter¹ in 1896 observed a reduction in the number of drops in the outflow from opened coronary veins. He postulated efferent vasoconstrictor neurones in the vagus trunk and their origin from the medulla oblongata.

The somatic vasoconstrictor nerves arise from the central nervous system in the thoracolumbar cord and course through the anterior roots of the spinal nerves, via the white rami communicantes to the sympathetic chain ganglia and by devious and often quite indirect paths to their peripheral distribution. The vagus is a cranial parasympathetic nerve; the presence of vasoconstrictor neurones to the coronaries via the vagus forms an unexpected exception to the general course of vasoconstrictor distribution to other regions of the body.

In an earlier paper² evidence is given showing that the reaction of the coronary blood vessels to cervical vagosympathetic stimulation in the dog is unpredictable in that it is sometimes constrictor and sometimes dilator in effect. Close physiological and morphological association between the paths of the efferent dilator and the constrictor neurones to the body in general suggest a similar common central origin for the neurones distributed to the coronaries. A plausible hypothesis is that the neurones of each of these pathways may arise in the thoracic cord, and the postganglionic neurones of each be distributed from the sympathetic ganglia, even as high in the chain as from the superior cervical ganglion. The reactions reported in the literature to tests in the normal animal applied to the midcervical region of the vagosympathetic trunk are about as readily explained on the assumption of a thoracic origin as on a vagal origin of the coronary constrictors.

From the Department of Physiology of the University of Missouri.

*This report is based on the study of two series of dogs. The writer is indebted to the Institute for Medical Research of the Mayo Foundation for the facilities of the institute in the preparation and study of the first group of these animals.

I am deeply grateful for the assistance of the director, Dr. Frank C. Mann, and of Dr. Hiram E. Essex and the laboratory staff. Dr. Mann kindly operated upon the dogs, and Dr. Essex and the laboratory staff gave untiring support during their physiological testing. The second series was operated upon and tested in the laboratories of the University of Missouri. Grateful acknowledgment is extended to Dr. Robert W. Siddie and Dr. James A. Atkins and the junior members of the staff for aid both in the surgery and the physiological testing of this series.

†A research grant from the National Research Council has covered part of the expense of calculating and tabulating the voluminous data from these tests. Sincere appreciation of this scientific aid is hereby recorded.

A definitive test devised to establish conclusively the true origin and pathway of distribution of the coronary vasoconstrictor neurones is the experimental task we have undertaken in the present research.

ELIMINATION OF THE CORONARY CONSTRICTOR NEURONES BY DEGENERATION OF THE VAGUS TRUNK

The only conclusive procedure to prove the hypothesis of vagal origin is the complete removal of vagal neurones from the common vagosympathetic pathways. This can be accomplished by the process of surgical interference and physiological degeneration, followed by analytical experiments applied to the nerve trunks after the degenerative loss of the efferent group of vagal neurones.

We have sectioned the vagus between the ganglion nodosum and the exit of the vagus roots from the jugular foramen. This is the operation used by Morgan and Goland,³ and by Heinbecker and O'Leary.⁴ Vagotomy was carried out aseptically on dogs under ether. Unilateral transections were done central to the ganglion nodosum, leaving one vagus intact for later experimental comparisons. The superior cervical ganglion of the side operated upon was also freed at the time of the vagotomy and the two closely bound ganglia transposed out of their normal positions as a drastic check on the cutting of all rootlets.

Animals were tested for evidence of nerve control of the coronary flow after varying operative intervals of from 8 to 188 days. The right vagus was usually sectioned. Dogs survive this unilateral operation well and are in good physical condition for the final functional tests.

METHODS OF TESTING CORONARY NERVE CONTROL AFTER DEGENERATION OF THE VAGUS

Coronary control after degeneration of the vagus was tested by stimulation of the peripheral cervical vagosympathetic, or the cardiac nerves in the thorax, and recording the reactions in terms of variations in the rate of flow of blood from the coronary sinus. The experimental tests were done with open chest under ether anesthesia, with heparin to prevent clotting of blood. The arterial pressure was equalized and recorded as described in a previous paper.²

The experimental sequence was as follows: First, the unoperated cervical vagosympathetic was stimulated for evidence of the presence of normal inhibitory vagus neurones. A positive reaction of inhibition was accepted as proof that the degenerated vagus originally contained a similar quota of active inhibitory neurones.

The degenerated vagus was then tested for cardiac inhibitory fibers. The failure of inhibitory response is the most sensitive physiological proof of the completeness of degeneration of efferent vagal neurones. The crucial experiment for which these steps are purely preliminary is

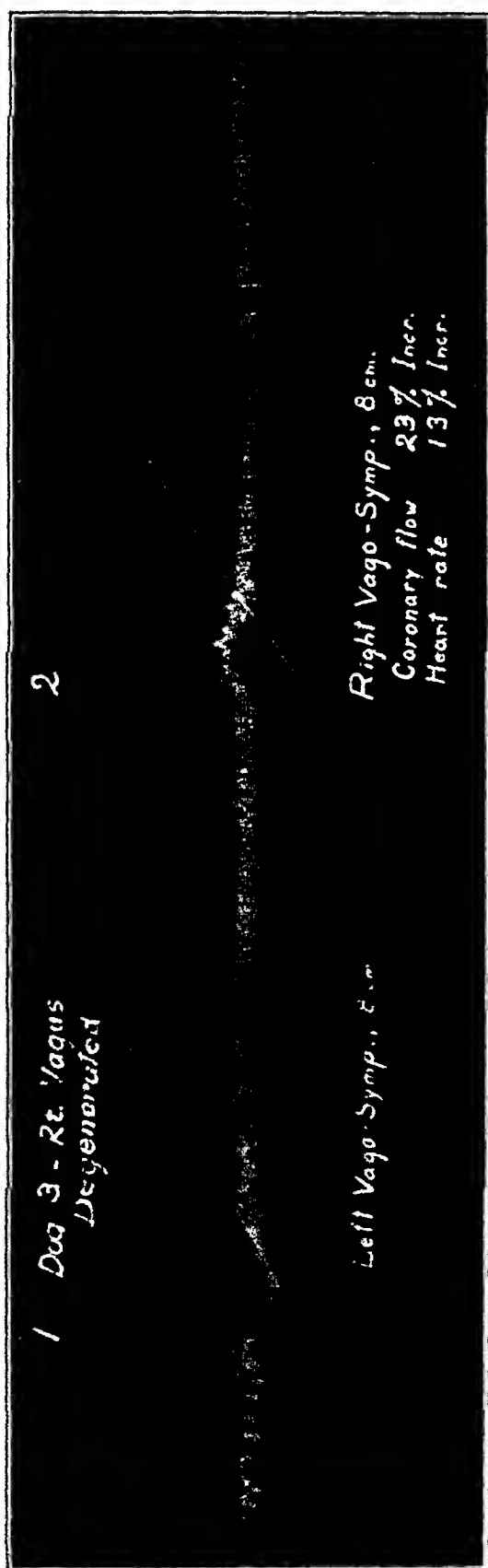


FIG. 1.—DOG 3. Test 1: Presents the usual vascular responses to stimulation of the normal vagosympathetic of the dog. The blood pressure is controlled, hence shows only immediate reaction changes. The coronary dilation in the after-period is largely reflex.

Test 2: Gives the responses of the right vagosympathetic after the vagus was cut above the ganglion nodosum and the vagal neurones had degenerated. It is assumed that the cardiac acceleration and coronary dilation of 23 per cent are due to the stimulation of cervical sympathetic neurones which are not now opposed by vagal constrictor and inhibitor neurones. The experiment should be compared with that of FIG. 2. Time in 5-second intervals. Stimulus from a Harvard Inductorium supplied by one dry cell. (Reduced to 46 per cent of original size.)

the test for coronary constriction. It seemed to the author that negative inhibitory evidence would strengthen the value of the method of degeneration in the study of the nerve control of coronary constriction.

PROTOCOL I

Dog 3. Test 1: Stimulating the left vagosympathetic above inferior cervical ganglion, 8 cm.

TIME	BLOOD PRESSURE	PER CENT CHANGE	HEART RATE	PER CENT CHANGE	CORONARY FLOW	PER CENT CHANGE
10" before	87.0		126		36	
4" after	31.0		Heart Inh. 4 sec. Flow stopped 3 sec.			
10" after	79.0	-9	144	14	32	-11
20" after	85.0	-2	126	0	36	0
30" after	89.0	2	126	0	38	6
45" after	91.0	4	132	5	42	17
60" after	94.0	8	132	5	42	17
80" after	93.0	7	126	0	41	14
90" after	91.0	4	126	0	39	8

Test 2: Stimulating right degenerated vagosympathetic above the inferior cervical ganglion, 8 cm.

10" before	89.0		126		39	
10" after	100.0	12	144	14	48	23
20" after	93.5	5	129	2	44	13
30" after	93.6	5	126	0	42	8
45" after	93.0	5	126	0	42	8
60" after	91.5	3	126	0	41	5
90" after	93.0	5	126	0	42	8

CORONARY RESPONSE TO CERVICAL VAGOSYMPATHETIC STIMULATION AFTER VAGAL DEGENERATION

Complete loss of coronary constriction was the typical response to stimulation of the operated cervical vagus. Inhibitory control of the heart rate was also lost in every degenerated nerve examined, always present in the normal unoperated vagus. The data on the heart rate alone support the efficiency of the degeneration method in application to the problem of coronary control. The complete disappearance of coronary constriction after the vagus was cut and allowed to degenerate is conclusive proof that the constrictor fibers are true efferent vagal neurones. We have pursued the problem by further analytical tests in search of other pathways. All such experiments have been relatively, but not exclusively, negative.

Dogs vary greatly among themselves in the mass and course of their cardiac neuronal architecture. This fact accounts in some degree for certain seemingly contradictory experimental data. In certain animals, Animal 7, Test 6, Fig. 2, there was no visible response of any kind to cervical vagosympathetic stimulation in the degenerated nerve. This is in exact contrast to Animal 3, Test 2, Fig. 1, in which stimulation of the degenerated vagus (cervical vagosympathetic) yielded both coronary dilation and cardiac acceleration. The failure of coronary responses in the degenerated vagus of Animal 7 is an example of individual variation. This particular dog had lost its coronary constrictor and

cardiac inhibitory neurones by degeneration and never did possess cervical sympathetic neurones of either dilator or accelerator type. In Animal 3 both groups of neurones were present in the corresponding region of the vagosympathetic trunk. The possibility of coronary dilator neurones in the operated trunk must be eliminated from the cervical field before final proof of complete degeneration of coronary constrictor nerves can be made.

PROTOCOL II

Dog. 7.—Wt. 8.8. kg. Tested 107 days after vagosection above the ganglion nodosum. Heparin; 50 mg. per kilogram. Donor blood used. Blood pressure uniform.

Test 6: Stimulating the right vagosympathetic, 5 cm. above the inferior cervical ganglion, 6 cm.

TIME	BLOOD PRESSURE	PER CENT CHANGE	HEART RATE	PER CENT CHANGE	CORONARY FLOW	PER CENT CHANGE
10" before	75.4		156		45.9	
30" after	70.5	- 7	156	0	46.8	2
60" after	68.7	- 9	156	0	45.5	-1
90" after	66.4	-12	156	0	46.4	1
120" after	67.1	-11	156	0	45.3	-1
150" after	67.1	-11	156	0	44.5	-3
180" after	68.7	- 9	156	0	44.8	-2

Test 7: Stimulating the right inferior cervical ganglion, 6 cm.

15" before	68.7		156		44.8	
15" after	74.5	8	252	62	75.4	68
30" after	66.1	-4	192	23	65.0	45
45" after	64.1	-7	174	12	51.6	13
60" after	64.1	-7	168	8	48.5	8
75" after	66.0	-3	168	8	45.2	1
90" after	66.6	-3	168	8	44.9	0
120" after	68.4	0	168	8	44.1	-2
150" after	67.5	-2	168	8	43.0	-4
210" after	73.0	6	162	4	41.3	-6

Nicotine was injected into the inferior cervical ganglion in each of two operated dogs in order to remove the masking effects of sympathetic reactions on any possible undegenerated inhibitory or constrictor neurones. Upon stimulating the cervical vagosympathetic trunk one animal yielded no variations from the previous dilator reactions. The other animal gave a mild degree of coronary constriction, Dog. 4, Tests 26 and 27. The tests demonstrate that a mild degree of coronary constriction may become evident only when the masking dilator reactions are removed.

The amount of coronary constriction observed in Animal 4 was little more pronounced than the allowable factor of error in measurement, and yet too great to discard. On the whole, we give weight to this evidence as indicating the occasional presence of a comparatively few neurones of the efferent coronary constrictor type lying in the ganglion nodosum or adjacent vagus trunk. The assumption of a slight degree of embryonic dispersion by centrifugal migration of the neuroblasts of the neural crest which gives rise to the coronary constrictor center is indicated.

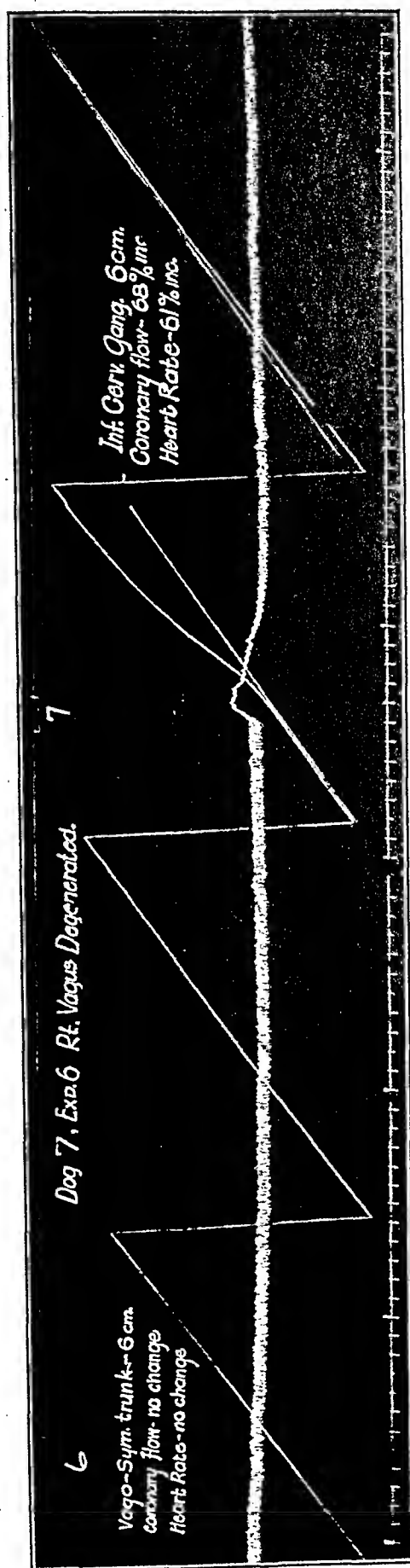


Fig. 2.—Dog 7. Test 6: Shows complete absence of any response to stimulation of the cervical vagosympathetic trunk, 6 cm. The conclusion is drawn that neither coronary dilator nor coronary constrictor fibers are present in the cervical trunk of this particular animal. It is to be compared with Fig. 1, Test 2.

Test 7: When the electrodes were applied to the inferior cervical ganglion, with the same strength, 6 cm., a voluminous coronary dilation promptly occurred. The coronary flow increased 68 per cent. There is a corresponding increase in cardiac rate, but the relationship is not causal. (Reduced to 58 per cent.)

EVIDENCE OF CORONARY DILATOR NEURONES IN THE CERVICAL SYMPATHETIC
AFTER DEGENERATION OF THE VAGUS

Degeneration of the coronary constrictor and of the cardiac inhibitor neurones prepares a simplified structure on which to search for the presence of antagonistic coronary dilator as well as cardiac accelerator pathways in the cervical sympathetic trunk. Table II of an earlier paper² presents evidence for the presence of neurones of the dilator group obtained from tests complicated by the simultaneous reactions of coronary constrictor neurones in the cervical vagosympathetic trunks of normal unoperated animals.

TABLE I
CERVICAL VAGOSYMPATHETIC STIMULATION AFTER DEGENERATION OF THE VAGUS

ANIMAL AND TEST NO.	STRENGTH OF STIM. IN COIL POSITION (CM.)	TIME FROM BE- GINNING OF STIM. (SEC.)	PER CENT OF CHANGE			POINT OF STIMULATION OF VAGOSYMPATHETIC
			BLOOD PRES- SURE	HEART RATE	CORO- NARY FLOW	
1—6	6	40	-1	2	12	Nodosal and sup. cerv. gang.
1—9	6	45	-1	0	9	Nodosal and sup. cerv. gang.
2—16	6	30	0	2	-4	Nodosal and sup. cerv. gang.
		90	1	0	-9	
6—12	4	30	1	0	-10	Nodosal and sup. cerv. gang.
5—8	4	35	-1	-2	-9	Just below nodosal and sup. cerv. gang.
4—14	4	15	5	25	18	Midneck
		30	-3	6	1	
5—6	6	15	-1	6	14	Midneck
6—7	6	15	-1	0	30	Midneck
		30	-1	-4	44	
		90	-6	-7	63	
6—22	6	20	-1	2	-4	Midneck
		40	0	5	8	
10—12	4	20	0	31	22	Midneck
5—31	4	20	1	22	18	3 cm. above inf. cerv. gang.
		30	0	7	1	
		120	-3	0	26	
7—3	8	30	2	-4	2	3 cm. above inf. cerv. gang.
		120	-2	-4	10	
9—49	4	30	1	0	-2	3 cm. above inf. cerv. gang.
		60	1	0	-2	
3—2	8	10	12	14	23	2.5 cm. above inf. cerv. gang.
		30	5	0	8	
		60	3	0	5	
5—39	4	25	9	46	19	1.5 cm. above inf. cerv. gang.
		60	0	2	-4	

Stimulation of the vagosympathetic between the superior and inferior cervical ganglia after degeneration of the vagus generally produces coronary dilation (Fig. 1, Test 2). The reaction is more profound when the stimulus is applied to the trunk near the inferior cervical ganglion. In fact, as already stated, it sometimes fails at the middle of the trunk or toward the superior cervical ganglion (Fig. 2, Test 6).

Complete analysis of the problem presented is more difficult than at first appears. The location of the postganglionic cells of the few coro-

nary dilator fibers which form a pathway above the inferior cervical ganglion has been assumed to be in the superior cervical ganglion. The bundles of postganglionic fibers run down the cervical vagosympathetic toward the heart and should be available for stimulation and give approximately the same volume of reaction wherever stimulated along their cervical course. This hypothesis did not stand the test of experimental proof in two particulars: First, the coronary dilator reaction sometimes failed altogether in the midcervical trunk, and second, the volume of coronary dilation was greater when the stimulus was applied near the inferior cervical ganglion.

Simultaneous stimulation of the ganglion nodosum and the superior cervical sympathetic ganglion, or of the cervical vagosympathetic in the upper neck area of the operated vagus, produced only slight coronary effects. Sometimes there is mild constriction, as in Dog 2, Test 16, or coronary dilation, as in Dog 1, Tests 6 and 9, or no effects at all, as in Dog 7, Test 6 (Fig. 2). Such seemingly contradictory data are to be anticipated in consideration of the possibility of complete absence of, or variation in numbers of, superior cervical coronary dilator neurones, in combination with an equally variable number of undegenerated coronary constrictor neurones outside the medullary center.

The coronary dilation in response to cervical stimulation may range from 0 to 30 per cent if the vagus is degenerated, depending upon the location of the point stimulated. If the isolated superior cervical sympathetic ganglion is stimulated, the coronary dilation is not so massive and sometimes fails, a fact which argues for few, and in some animals no, neurones in the superior cervical reflex arc. This explains Fig. 2, Test 6, in that this animal had no cervical dilator and no accelerator neurones, and no coronary constrictor neurones distal to the point of vagosection, hence its reactions were quite negative.

EVIDENCE OF DILATOR REACTION BY WAY OF A MIDDLE CERVICAL MICROGANGLION AFTER DEGENERATION OF THE VAGUS

If the point of stimulation is moved along the cervical vagosympathetic toward the inferior cervical ganglion, the amount of dilation becomes greater. In midcervical stimulation of Dogs 4 and 5 coronary dilation was slight, though in Dog 6, Test 7, it was greater. These are examples of mass variation of each of these two groups of cervical nerves among individual animals. The reaction of each group is small, but one's inability to determine to what extent each is present is sufficient to confuse the judgment upon the total significance of the data from the normal animal.

If the electrodes are placed on the cervical trunk within 2 cm. of the inferior cervical ganglion, there is a stronger coronary dilator reaction. Extrapolar stimulation may be ruled out. The observed responses suggest ganglionic synapses in the vagus trunk at this region.

There is gross anatomical evidence of a middle cervical ganglion in about 1 per cent of the dogs that come to autopsy. The greater dilation upon stimulation just above the inferior cervical ganglion in Animal 5 was explained by histological confirmation from sections of the vago-sympathetic trunk of the area stimulated. Chains of nerve cells were found among the bundles of fibers for a short distance along the course of the trunk. Apparently the numbers of cell bodies of neurones of this type are not aggregated in sufficient mass for gross evidence of a ganglion. Nevertheless, their presence in sufficient quantity to serve as a microganglion on the efferent dilator pathway is established.

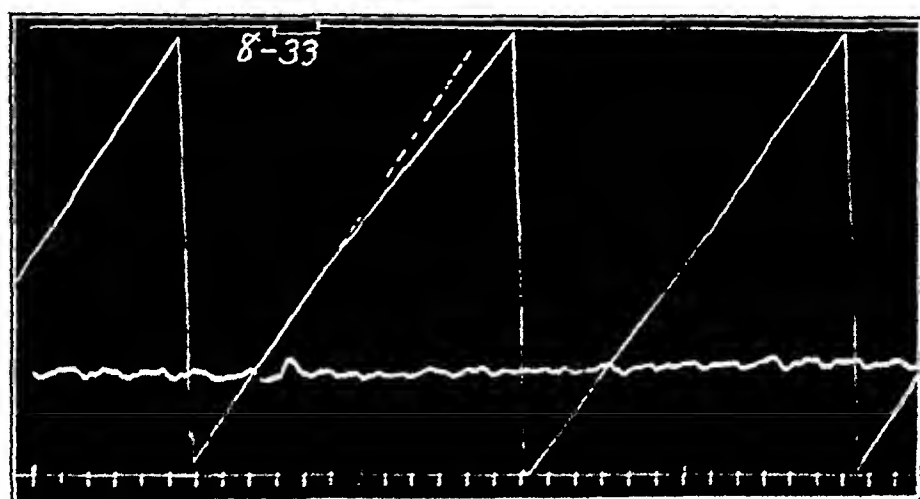


Fig. 3.—Dog. 8. Test 33: This record illustrates coronary constriction upon stimulating the superior cardiac nerve in the normal animal after atropine. (Reduced to 60 per cent.)

PROTOCOL III

Dog. 8.—Wt. 5.1 kg. Heparin, atropine. Had previously been injected with ephedrine and adrenalin.

Test 33: Stimulation of the right superior cardiac nerve of the normal animal, 6 cm.

TIME	BLOOD PRESSURE	PER CENT CHANGE	HEART RATE	PER CENT CHANGE	CORONARY FLOW	PER CENT CHANGE
10" before	37.0		207		90.0	
15" after	36.0	-3	213	3	78.0	-13
30" after	37.5	1	213	3	76.0	-16
60" after	39.0	5	213	3	82.0	-9
120" after	41.0	11	213	3	91.6	2
165" after	41.0	11	213	3	96.0	7

CORONARY RESPONSE OF THE SUPERIOR AND INFERIOR CARDIAC NERVES BEFORE AND AFTER DEGENERATION OF THE VAGUS

The cardiac nerves at and below the inferior cervical ganglion of the dog are mixed trunks. The gross anatomy of the relations of the inferior cervical ganglion and vago-sympathetic trunk and the origin of the cardiac branches which these contribute to the cardiac plexus were described in the dog by Schmiedeberg⁵ in 1871, Pavlov⁶ in 1887, and

Keng⁷ in 1893. Schmiedeberg demonstrated the presence of cardiac inhibitor and accelerator neurones in these nerves, but coronary neurones were then unknown.

The superior cardiac nerve from the inferior cervical ganglion, the *nervus cardiacus superior* of Schmiedeberg, is the main trunk from the vagosympathetic complex to the cardiac plexus. It arises either directly out of the inferior cervical ganglion or from the ganglion and trunk in common with the recurrent laryngeal, from which it quickly separates as an independent nerve. It contains coronary neurones inseparably mixed with the cardiac neurones in varying proportions.

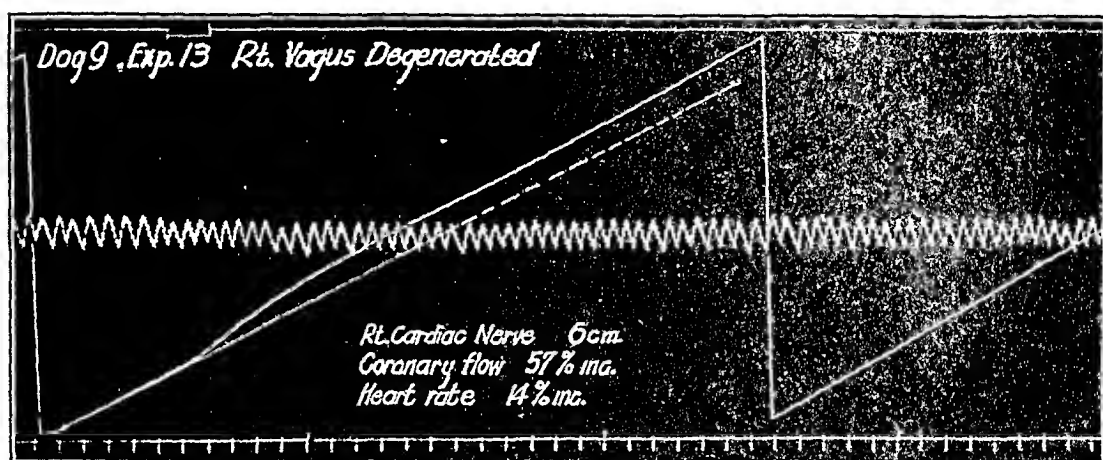


Fig. 4.—Dog 9. Test 13: Reaction of the coronary flow to stimulation of the right superior cardiac nerve, 127 days after vagosection above the ganglion nodosum. The coronary dilation shows a prompt increase of 57 per cent, lasting for only a few seconds, as contrasted with the dilation shown in Fig. 2, Test 7. (Reduced to 54 per cent.)

PROTOCOL IV

Dog 9.—Wt. 10.7 kg. Heparin 60 mg. per kilogram. Blood pressure equalized. Donor blood used.

Test 13: Stimulation of the superior cardiac nerve, a branch of the recurrent laryngeal about 1 cm. from the inferior cervical ganglion.

TIME	BLOOD PRESSURE	PER CENT CHANGE	HEART RATE	PER CENT CHANGE	CORONARY FLOW	PER CENT CHANGE
15" before	85.0		162		31.1	
12" after	85.0	0	180	11	48.9	57
30" after	83.5	-2	156	-4	38.5	24
45" after	83.0	-2	156	-4	31.3	1
75" after	84.0	-1	156	-4	31.2	0
105" after	84.5	-1	156	-4	34.0	9
150" after	84.0	-1	156	-4	34.0	9
210" after	85.5	1	156	-4	34.2	10

Stimulation of the *nervus cardiacus superior* in dogs having a normal vagus but treated with atropine usually produces coronary constriction. But at times coronary dilation predominates. Figure 3 presents the coronary constrictor type of reaction under these conditions. The decrease in flow from the coronary sinus amounted to 16 per cent in the test figured.

Stimulation of the superior cardiac nerve after the vagus nerve has degenerated never produces coronary constriction, but does induce a pronounced coronary dilation of 50 to 60 per cent and more. In Animal 9, Test 13, Fig. 4, the dilation amounted to a 57 per cent increase in the flow from the coronary sinus. One rarely secures such extreme coronary dilation in response to stimulation of the normal mixed cardiac nerve because of the neutralizing effects of antagonistic neurones. The volume of dilation obtained in the absence of coronary constrictor neurones is, therefore, the best graphic measure of the total available reflex dilation in the normal animal.

Stimulation of the superior cardiac nerve in the normal animal before atropine also produces very pronounced cardiac inhibition. In the atropinized animal inhibition is lost, and coronary constriction and

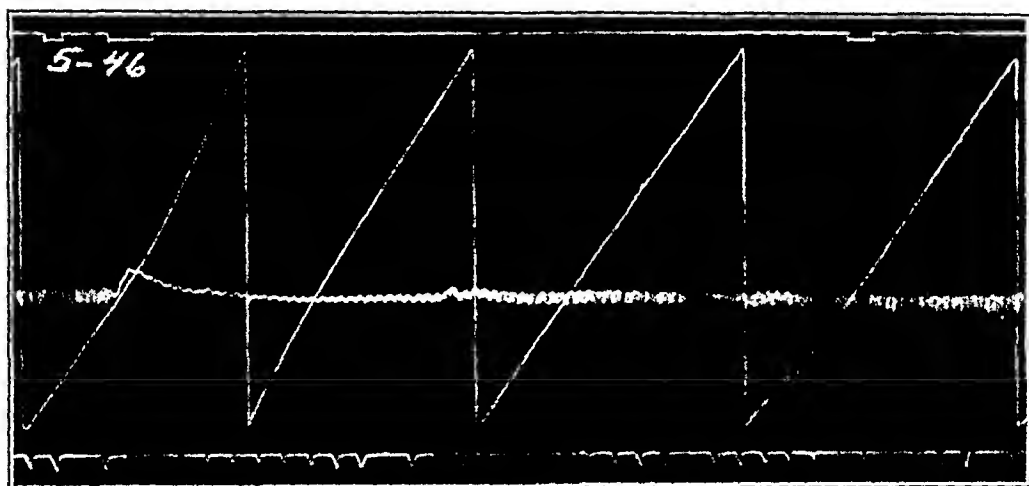


Fig. 5.—Dog 5. Test 46: Increase of the coronary flow upon stimulating the inferior cardiac nerve arising out of the spray of filaments below the right inferior cervical ganglion, 4 cm. The right vagus was cut 22 days earlier. (Reduced to 50 per cent.)

cardiac acceleration are present. After vagus degeneration, coronary dilation and cardiac acceleration remained as shown in Dog 9, Test 13, Fig. 4. These reactions offer a convenient and decisive analysis of the physiological content of the terminal cardiac pathways.

We have obtained responses similar to the above from stimulation of the total vagosympathetic trunk and from a group of small nerves just below the inferior cervical ganglion (Fig. 5, Dog 5, Test 46).

The superior cardiac nerve of the dog is indeed the chief efferent pathway for the constrictor control of the coronary arteries. Although some constrictor fibers are present in the *nervus cardiacus inferior* most of the coronary constrictor neurones run in quite direct course from their origin in the medulla down the vagosympathetic sheath, through the inferior cervical ganglion into the superior cardiac nerve and reach

PROTOCOL V

Dog 5.—Wt. 13.5 kg. Blood pressure equalized. Right vagus sectioned above the ganglion nodosum, twenty-two days before testing. The superior sympathetic ganglion not isolated from its peripheral branches.

Test 46: The main division to the cardiac plexus from the spray of nerves arising just below the inferior cervical sympathetic ganglion was stimulated 4 cm.

TIME	BLOOD PRESSURE	PER CENT CHANGE	HEART RATE	PER CENT CHANGE	CORONARY FLOW	PER CENT CHANGE
10" before	65.5		174		88.4	
20" after	68.0	4	324	86	141.6	60
50" after	64.0	-2	249	43	103.4	17
75" after	65.0	-1	204	17	96.8	10
120" after	65.5	0	180	3	90.0	2
160" after	62.0	-5	174	0	95.4	7

their distribution in the coronary blood vessels via the cardiac plexus. After degeneration of the vagus there is left unopposed the entire pattern of the coronary dilator system.

In the absence of the great mass of coronary constrictor neurones, it has been easier to follow the course of the dilators from their origin in the thoracic spinal cord, through the sympathetic system in the great fanlike spread from the superior cervical sympathetic to the sixth thoracic spinal ganglion, and via the branches of these ganglia also through the constituents of the cardiac plexus to the coronary vessels. A very interesting part of this body of information is the doubling back within the vagosympathetic paths of the postganglionic neurones of the middle and superior cervical ganglia. One may assume that in man the postganglionic neurones run in the superior and middle cardiac nerves, which in the human arise from the superior and middle cervical ganglia.

The presence of nerve cells along the course of the lower cervical sympathetic trunk of the dog that are clearly homologous with the middle cervical ganglion seems not to have been recorded hitherto in the literature.

SUMMARY

1. Vagosection was performed above the ganglion nodosum. The animals were allowed to recover and the nerves to undergo a variable period of degeneration and repair after which functional tests were applied.

2. Dogs with vagosection exhibit a total, or almost total, loss of coronary constriction in response to cervical vagosympathetic stimulation. Two animals have shown a mild degree of coronary constriction after cervical dilator control was reduced by injections of nicotine into the cervical sympathetic ganglia.

3. These more distally placed coronary constrictor neurones have only a moderate total effect and are not always present. A satisfactory

explanation of this occasional type of animal is that some few neuroblasts have migrated distally in early embryonic development.

4. The loss of coronary constriction after vagotomy and degeneration indicates that the vagus is the sole pathway of the efferent coronary constrictor nerves.

5. After the coronary constrictors are degenerated, stimulation of the cervical vagosympathetic produces coronary dilation of variable amount.

6. Coronary dilation from stimulation of the cervical vagosympathetic trunk after vagal degeneration does not occur in all animals, and varies in amount from nothing to a medium degree of dilation among those animals in which it is present.

7. There is greater reaction to stimulation of the lower cervical region just above the inferior cervical ganglion. A definite palpable middle cervical ganglion is rarely present in the dog. Histological sections, however, show that strands of nerve cells may be present among the bundles of axones of the vagosympathetic trunk at approximately the region of the middle cervical ganglion. These cells function as links in the chain of efferent coronary dilator pathways.

8. Cardiac inhibitory fibers were completely absent from the degenerated vagi of the animals reported in this series.

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THE TEMPERATURE OF THE FLARE AS AN INDEX OF THE INTENSITY OF THE HISTAMINE SKIN REACTION*

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THE histamine skin reaction is used widely as a test of circulatory efficiency in the study of peripheral circulatory disturbances. In 1927, Thomas Lewis¹ demonstrated that it consists of three distinct responses: (1) a local dilatation of the capillaries which causes a purplish areola about the site of introduction into the skin, (2) an increased capillary permeability which results in a wheal at the site of injection, and (3) a dilatation of the surrounding arterioles which is visible as a red flare. Since that time it has been firmly established as a valuable test of local circulatory efficiency.² The technic of the test has been modified since it was first described by Lewis. As now performed by us,³ it consists of an intradermal injection of a 1:2,000 solution of histamine in 0.5 per cent novocaine in an amount sufficient to produce a wheal 2 mm. in diameter. Normally a purplish border 1 mm. in width appears within from 20 to 30 seconds around this primary wheal. In from 1 to 2 minutes there is an irregular increase in the size of the primary wheal to form a secondary wheal. A flare about 3 cm. in diameter makes its appearance in about 2 minutes and gradually increases in intensity, reaching its height in 10 minutes. The use of the novocaine with the histamine makes the test painless without altering the intensity of the reaction.

The usual criterion of the intensity of the histamine reaction is the rapidity of the development and the intensity of the flare. We have noticed that in normal individuals there are marked variations in the size and visible intensity of the flare which depend to a certain extent upon whether the skin is light or dark, and hairy or nonhairy. In negroes, for example, it is almost impossible to read the flare reaction. This test, furthermore, suffers as a standard of circulatory efficiency since the grading of the intensity of the flare is a matter of opinion, and the reading varies with each examiner.

These difficulties led us to search for a more objective means of determining the intensity of the histamine flare and thus of estimating the efficiency of the skin circulation. The determination of the temperature change in the area of the flare appeared to us to be a more accurate and objective measure of the histamine skin reaction. Since the temperature of the skin is dependent upon the circulation within the skin when all

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other factors such as room temperature, etc., are kept constant, the measurement of the temperature of the flare should eliminate such variables as the color and hairy distribution of the skin and the visual acuity of the examiner and should thus standardize the grading of the histamine skin reaction.

METHOD

Studies were made in both upper and lower extremities in twelve normal individuals of various complexions and in eight individuals with peripheral circulatory disturbances. These tests were made in a room at constant temperature (20 to 22° C.). The individuals were examined while resting horizontally. The areas to be examined were marked, and their temperatures were taken with a mercury skin thermometer every five minutes until several readings were constant. Sufficient solution (1:2,000 histamine in 0.5 per cent novocaine) was then injected intradermally in the marked areas to make a wheal 2 mm. in diameter. The temperature of the flare that resulted was measured every five minutes, and its visible intensity was noted until it began to disappear.

OBSERVATIONS

The averaged results obtained in twelve normal individuals are shown in Table I. In each case, as in the typical normal record shown in Table II, the temperature curve of the flare rose very rapidly in the

TABLE I
AVERAGED MAXIMUM TEMPERATURE OF HISTAMINE FLARES IN NORMAL INDIVIDUALS*

		3 BLOND FEMALES	3 BLOND MALES	3 BRUNET MALES	3 NEGRO MALES
Above elbow	Visible intensity	4	4	4	2
	Temperature	34.8	34.6	33.6	33.8
Below elbow	Visible intensity	4	4	4	2
	Temperature	34.0	34.2	33.4	33.8
Above wrist	Visible intensity	4	4	4	2
	Temperature	33.8	33.8	33.2	33.6
Dorsum of hand	Visible intensity	4	4	4	2
	Temperature	34.2	34.0	34.2	34.0
Dorsum 3rd finger	Visible intensity	4	4	4	2
	Temperature	34.0	33.6	33.6	33.6
Above knee	Visible intensity	4	4	4	2
	Temperature	34.0	33.8	33.6	33.4
Below knee	Visible intensity	4	4	4	2
	Temperature	33.8	33.8	33.0	33.2
Above ankle	Visible intensity	4	4	4	2
	Temperature	33.0	33.2	33.4	33.4
Dorsum of foot	Visible intensity	4	4	4	2
	Temperature	33.0	33.0	32.4	32.6

*Temperature in centigrade scale; visible intensity 1 = grade plus 1, 2 = grade plus 2, etc.

first 5 minutes, then slowly until it reached its height in 15 to 20 minutes after the injection. It was sustained at this level for 5 to 20 minutes and then dropped slowly to normal in from 60 to 120 minutes. The

visible flare reaction was similar, although in the brunets and negroes it was not so marked as in individuals of lighter complexion. The temperature of the flare, however, rose in these individuals, as it did in the other normals in whom there was a marked visible flare. In several instances in the negroes there was a rise in the temperature of the skin around the site of injection of the histamine even in the absence of a visible flare.

TABLE II

COMPARISON OF THE VISIBLE INTENSITY AND THE TEMPERATURE OF THE HISTAMINE FLARES IN A NORMAL BRUNET MALE

		0	5'	10'	15'	20'	25'	30'	45'
Above elbow	Visible intensity		4	4	4	4	4	4	3
	Temperature	30.6	32.6	33.2	33.8	33.8	33.0	33.2	31.8
Below elbow	Visible intensity		4	4	4	4	4	4	3
	Temperature	30.2	32.0	32.8	33.2	33.4	32.8	33.0	31.4
Above wrist	Visible intensity		4	4	4	4	4	4	3
	Temperature	29.2	32.2	32.8	33.2	33.4	33.0	33.0	31.4
Dorsum of hand	Visible intensity		3	3	4	4	4	4	3
	Temperature	29.6	32.0	33.0	33.8	34.0	33.8	33.2	31.6
Dorsum 3rd finger	Visible intensity		3	3	4	4	3	3	3
	Temperature	29.0	32.0	32.8	33.8	34.0	33.6	33.0	31.4
Above knee	Visible intensity		3	4	4	4	4	4	3
	Temperature	30.8	33.0	33.0	33.8	33.6	33.4	33.0	32.0
Below knee	Visible intensity		3	3	4	3	3	3	3
	Temperature	30.0	32.0	32.6	33.0	33.0	32.4	32.4	31.0
Above ankle	Visible intensity		2	3	3	3	3	3	2
	Temperature	29.0	32.4	33.0	33.2	33.4	33.4	33.2	30.0
Dorsum of foot	Visible intensity		3	3	3	3	3	3	2
	Temperature	27.8	31.0	31.8	32.4	32.4	32.4	32.0	28.2

The temperature of the flares at the height of the reaction varied from 32.8-34.6° C. (33.6° C. av.), on the dorsum of the hand and fingers, to 33.8-35.0° C. (34.6° C. av.), above the elbow. In the lower extremities the temperature varied from 31.2-33.0° C. (32.0° C. av.), on the dorsum of the foot, to 33.0-34.2° C. (33.6° C. av.), above the knee. The temperatures in blond females and males averaged from 0.5 to 1.0° C. higher than those of brunets and negroes.

TABLE III

COMPARISON OF HISTAMINE FLARES IN NONHAIRY AND HAIRY SKIN OF FOREARM IN A NORMAL BRUNET MALE

		0	5'	10'	15'	20'	25'	30'
<i>Volar Surface (Nonhairy)</i>								
Above elbow	Visible intensity		3	4	4	4	4	4
	Temperature	30.4	32.2	33.0	33.8	33.8	34.0	34.0
Below elbow	Visible intensity		3	4	4	4	4	4
	Temperature	29.8	32.0	33.0	33.2	33.6	33.6	33.2
Above wrist	Visible intensity		4	4	4	4	4	4
	Temperature	29.2	32.2	32.8	32.8	33.2	33.2	32.6
<i>Dorsal Surface (Hairy)</i>								
Above elbow	Visible intensity		3	3	4	4	4	3
	Temperature	30.2	32.4	33.2	33.2	33.4	33.0	33.0
Below elbow	Visible intensity		3	3	4	4	4	3
	Temperature	30.0	32.2	32.8	32.8	33.4	32.8	32.8
Above wrist	Visible intensity		3	3	4	4	4	3
	Temperature	29.2	32.0	32.6	33.0	33.0	33.2	33.2

Table III is a comparison of the visible intensities and the temperatures of histamine flares in similar areas of hairy and nonhairy skin in the same individual. There was a definite lag in the development of the visible intensity of the flare in the hairy as compared to the nonhairy skin, but the temperature of the flares in the similar areas of skin rose to the same levels simultaneously.

To determine the reliability of our visible readings of the flare intensity as an accurate objective standard and index of the amount of blood in the skin, a list was made of the highest and lowest temperatures obtained in flares whose visible grade was from 1-plus to 6-plus. This is shown in Table IV. We found that the temperatures of the

TABLE IV
LOWEST AND HIGHEST TEMPERATURES OBTAINED IN FLARES OF VARIOUS GRADES OF VISIBLE INTENSITY

VISIBLE GRADE	TEMPERATURE (C.)	
	LOWEST	HIGHEST
Plus 1	27.2°	30.0°
2	27.6°	33.6°
3	29.4°	33.0°
4	32.0°	35.4°
5	34.4°	35.2°
6	33.0°	36.0°

various grades of visible intensities were not constant and that the difference between the lowest and highest temperatures of flares of a given visible intensity grade was as high as 6° C. In many cases flares of the same temperature were given visible grades differing as much as 3-plus. These marked variations in the grades of the visible flare reactions even when judged by one experienced in these tests, together with the presence of differences in the visible intensities of flares in hairy and nonhairy skin and the difficulty in reading the visible intensity in dark-skinned individuals, when compared with the uniformity and constancy of the temperatures of the flares, indicate that the temperature of the flare is a more definite and reliable index of the skin reaction to histamine than is its visible intensity.

The visible intensity and the temperature of the flares were then compared in 8 cases of peripheral circulatory disturbances, namely, 3 cases of arteriosclerosis, 3 cases of thrombo-angiitis obliterans, and 2 cases of vasospastic disease of the extremities. The results in a typical case of each of these three conditions are shown in Tables V and VI. In each of the six cases of organic vascular occlusion, as in the typical cases shown, the temperatures of the flares were within the normal limits determined above (Table I) in the parts of the extremity that had a normal circulation and below the normal limits in those parts in which the circulation was deficient. The circulatory efficiency was de-

TABLE V

COMPARISON OF THE VISIBLE INTENSITY AND THE TEMPERATURE OF THE HISTAMINE FLARES IN CASES OF ORGANIC VASCULAR OCCLUSION

		B. S.—THROMBO-ANGIITIS OBLITERANS				J. G.—ARTERIO- SCLEROSIS	
		RIGHT EXTREMITY (DISEASED)		LEFT EXTREMITY (NORMAL)			
		0	15'	0	15'	0	15'
Above knee	Visible intensity		4		4		3
	Temperature	30.4	33.2	30.4	33.6	30.8	33.0
Below knee	Visible intensity		4		4		2
	Temperature	30.0	33.0	30.2	33.2	30.8	32.2
Above ankle	Visible intensity		3		4		2
	Temperature	28.6	30.4	29.2	33.2	30.0	31.2
Dorsum of foot	Visible intensity		2		3		0
	Temperature	26.0	27.6	28.2	32.8	25.0	25.8

TABLE VI

COMPARISON OF THE VISIBLE INTENSITY AND THE TEMPERATURE OF THE HISTAMINE FLARES IN A CASE OF VASOMOTOR DISTURBANCE OF THE EXTREMITIES

		P. N. VASOMOTOR DISTURBANCE						
		0	5'	10'	15'	20'	25'	30'
Above elbow	Visible intensity		6	6	6	6	5	5
	Temperature	32.6	35.2	36.0	36.0	35.4	35.2	35.0
Below elbow	Visible intensity		6	6	6	6	6	5
	Temperature	32.4	34.4	35.2	35.6	35.2	35.0	34.4
Above wrist	Visible intensity		6	6	6	6	6	6
	Temperature	31.8	34.4	35.2	35.2	35.2	35.0	34.6
Dorsum of hand	Visible intensity		6	6	6	6	6	6
	Temperature	31.0	33.8	34.6	35.2	34.6	34.0	33.4
Dorsum of 3rd finger	Visible intensity		6	6	6	6	6	4
	Temperature	26.6	33.8	34.4	35.2	34.0	33.0	32.8

terminated by the subjective symptoms and the objective signs, which included arterial pulsations, the oscillometric index, the color and trophic changes in the skin, and the visible flare reactions. In the case of thrombo-angiitis obliterans (Table V) the circulation in the left lower extremity was determined to be normal. The right foot was red; trophic changes were present in the foot and in the lower one-third of the leg; the dorsalis pedis and posterior tibial pulsations were absent, and the oscillometric index in the foot was 0. In the diseased extremity the visible flare reaction on the dorsum of the foot was 2-plus, and the temperature of the flare rose only to 27.6° C. from a starting temperature of 26.0° C. In the upper part of the leg and in the thigh, where subjective and objective signs pointed to an efficient circulation, and in the normal left extremity the temperatures of the flares were within normal limits.

The patient with arteriosclerosis (Table V) had beginning gangrene of the toes. The temperature of the flare about the site of the histamine injection was only 25.8° C. on the dorsum of the foot, where the circulation was very poor; 31.2° C. above the ankle; and within the normal limits (33.0° C.) above the knee where the circulation was good.

The comparisons made in these six cases suggest that temperatures of flares which are below the established normals are indicative of deficient circulation.

In one case of vasomotor disturbance of the upper extremity (Table VI) the visible flare reactions and the temperature rise in the flare areas were greater than in our normal series. Although the starting temperature on the dorsum of the third finger was only 26.6°C ., the visible flare reaction at 15 minutes was 6-plus, and the temperature of the flare was 35.2°C . This marked reaction to histamine has been present in a few of the patients with vasomotor disturbance whom we have examined and will require further study for an explanation. In the other case of vasomotor disturbance of the extremities studied in this series, the temperatures of the flares were within normal limits.

SUMMARY

1. A. The temperature of the histamine flare reaches its height in 15 to 20 minutes.

B. The average temperature of the flares in the normal upper extremity varies from 33.6°C . on the dorsum of the third finger to 34.6°C . above the elbow, and in the normal lower extremity from 32.0°C . on the dorsum of the foot to 33.6°C . above the knee.

C. The temperature of the flare is from 0.5°C . to 1.0°C . higher in individuals with light complexions than in brunets and negroes.

D. In contrast to the visible intensity there are no appreciable differences between the temperatures of the flares in hairy and nonhairy areas.

2. The temperature of the flare is a more accurate index of the histamine skin reaction than is the visible intensity of the flare.

3. Failure of the temperature of the flare to rise to the above mentioned levels is suggestive of circulatory deficiency.

I wish to thank Dr. L. N. Katz for his advice in preparing this report.

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ALTERNATION PHENOMENA IN THE ELECTROCARDIOGRAM

OCCURRENCE IN A PATIENT WITH ACTIVE CAROTID SINUS REFLEX*

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ALTERNATION in strength of pulsations in the peripheral vessels (pulsus alternans) is a not uncommon clinical finding, long recognized, and in most instances considered by observers to suggest a poor prognosis. It may be detected by some type of photographic or mechanical recording device—more simply by the use of blood pressure cuff and stethoscope or, if marked, by palpation. Only rarely has it been associated with corresponding changes in the electrocardiogram.

Alternation of the various waves in the electrocardiogram may occur, and is usually unaccompanied by corresponding changes in the pulsation of the peripheral arteries.

Our patient has been studied for a period of about three and one-half years because of the occasional occurrence of convulsions and syncope. His electrocardiograms seemed unique in that they demonstrated alternation in the heights of the T-waves with changes in the intraventricular conduction. This phenomenon was found not only after premature contractions but also in the absence of premature contractions. In the absence of premature contractions, the electrical alternation was not associated with large pulse waves in the arteriogram. The patient had an extremely active carotid sinus reflex which manifested itself very strongly on his cardiovascular mechanism. At no time has the production of this reflex induced the alternation.

CASE REPORT

A. P., a white, sixty-three-year-old Polish janitor, with an unusually good health record, was found unconscious on the floor of the factory, Nov. 20, 1931. He had been an employee of the Eastman Kodak Company for eleven years when this study was started. His record at the medical department from 1920 to 1931 revealed a series of blood pressure determinations with systolic pressures varying from 140 to 180, and diastolic from 80 to 90 mm. On one occasion, in 1928, a few premature contractions were heard.

There was no history of trauma and no signs suggesting it. At all interviews and examinations conducted at intervals up to the date of onset he had been free from complaints. There was no history of previous "spells," dyspnea, precordial pain, palpitation, vertigo, or edema. He had been a moderately heavy user of alcohol, coffee, and tobacco. The family history was negative, and he denied all past illnesses. Because of the first attack of syncope, he was not permitted to return to work for one month.

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An examination three weeks later showed a well-developed male, weighing 156 pounds, and measuring 5 ft. 7 in. in height. There was no dyspnea, cyanosis, or edema. Ocular movements were normal. The eye balls were rather prominent, but there was no exophthalmus or lid lag. The pupils were normal, and the optic discs were well outlined. Evidence of moderate retinal sclerosis was seen. Marked pyorrhea alveolaris was present. There was evidence of pulmonary emphysema. The heart was not enlarged to percussion. The rhythm was regular, and there were no murmurs or thrills. The rate was 112 per minute; blood pressure was 130/80. An occasional premature contraction was heard. The abdomen was negative. Pulsus alternans was not detected when the blood pressure was taken.

The neurological examination was negative except for the occasional appearance of a coarse tremor of the extremities, noticed when the patient was perturbed. This seemed definitely under voluntary control.

Roentgenogram Examination.—Heart film at a distance of six feet showed a transverse type of heart and a widening of the shadow of the great vessels. Internal diameter of chest was 28.5 cm.; total transverse diameter of heart, 13.25 cm.; midline to left border, 10.0 cm.; midline to right border, 3.25 cm.; great vessels, 7.0 cm.

Skull examination, including roentgenography, was negative for evidence of fracture or other abnormalities. Stereoscopic films of the chest in 1922 showed evidence of inactive tuberculosis at both apices, and follow-up films of the chest showed no change (Dr. E. K. Richard).

The patient was taken to the Rochester General Hospital where he remained for three days. While there, his temperature varied from 99° to 101° F., he became irrational, threatened to jump from a window, and finally had to be restrained. During an examination, he suddenly emitted a cry, became spastic, and assumed the position of opisthotonos. His blood pressure, before the convulsion, was 158/80 and his pulse was 84. Afterward his blood pressure was 178/80; his pulse was not recorded. This episode lasted for five minutes, and during this time there was no loss of sphincter control. However, a bilateral positive Babinski reflex was noted, and there was a loss of the normal corneal reflex. The right extremities were slightly more spastic than the left, and the patient became very cyanotic. A short time later the mental aberration disappeared.

Laboratory Findings.—The blood Wassermann and Kahn tests were negative. Erythrocytes numbered 4,650,000; leucocytes, 6,000; and hemoglobin (Dare) measured 90 per cent. The blood smear was normal. Examination of the urine showed an absence of albumin and sugar, a negative sediment, and a specific gravity of 1.022. The blood sugar (fasting) was 102 mg. per cent; and blood nonprotein nitrogen was 32 mg. The spinal fluid pressure was 8 mm. Hg; the Pandy test was negative; spinal fluid sugar was 95 mg. per cent; no leucocytes were recognized, and 25 erythrocytes were counted per cubic millimeter. Cultures were sterile.

Course.—The patient remained symptom free until eight months later. He was seen at frequent intervals. During this time his blood pressure varied from 130 to 160 systolic and 84 to 102 diastolic. At this time a second period of unconsciousness occurred while he was attending his usual duties at the factory. An examination made a few minutes after the incident showed stertorous respirations and clonic movements of his lower jaw. The pulse rate was 96 and regular. His heart sounds were distant, and no murmurs were heard. There was a slight contusion behind his left ear. The patient was unable to account for either the first or second period of unconsciousness. He denied any recent overindulgence in alcohol, although he admitted that he had been taking small amounts regularly. Shortly after this, another attack of syncope occurred while the patient was at home. The patient was somewhat indefinite in his account of this last "spell."

Because of the hazard incident to his employment, he was retired from the company in February, 1933, and is now receiving a pension. He is able to do light work about the premises of his home.

DISCUSSION

We originally became interested in this patient because of our attempts to explain the cause of his syncope and convulsions. Numerous electrocardiograms, taken during the course of our investigation, showed alternation of certain of the complexes.

A rather extensive review of published tracings illustrating the phenomenon of alternation would seem to indicate that the findings encountered in this patient are unique. We have not found an identical

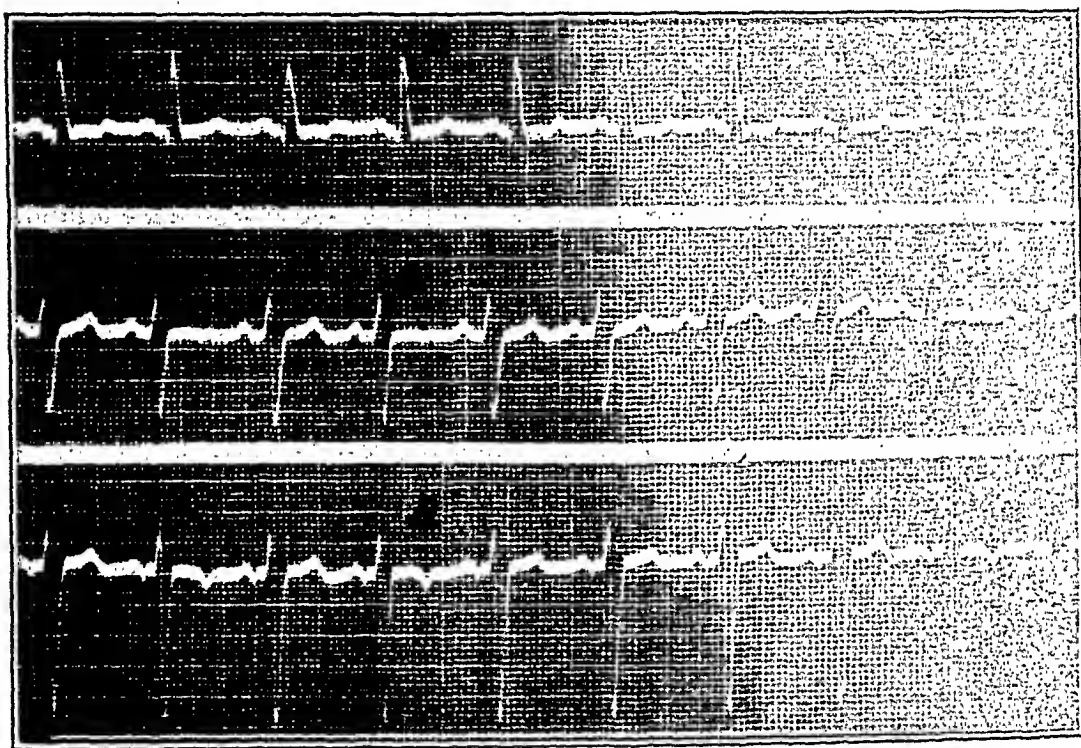


Fig. 1.—Leads I, II, and III, showing the rhythmic occurrence of electrical alternation. The unusual beats are marked *a*. The above periodicity repeated itself a number of times without interruption in all leads of the tracing taken on this date. Other tracings have shown alternation without the above periodicity. No premature contractions were encountered on this date.

record. The electrical alternation occurred in most of the thirty tracings taken during the three and one-half years of observation. Because of this apparent rarity, the case seemed deserving of a brief report.

The electrocardiograms of our patient showed predominant beats, characterized by a widening of the intraventricular conduction time (QRS measured 0.13 second to 0.14 second) (see Figs. 1, 2A, and 2B). There was slurring and notching of the QRS complexes in all leads. In addition to the above there were found unusual cycles characterized by a decrease in intraventricular conduction to 0.10-0.12 second with a change in the electrical axis of the T-waves. These unusual cycles were of two types and were classified according to the presence or absence

of changes in the arteriogram. We have designated these unusual cycles arbitrarily as *a* cycles or *b* cycles. The *a* cycles were not associated with a change in the arteriogram. The *b* cycles occurred after premature contraction and were associated with changes in the arteriogram.

A rhythmic occurrence of the unusual or *a* beats (see Fig. 1) was found on only one occasion. Premature contractions were not found in any of the three leads of this particular record (about 50 cycles in each lead were taken). When the cycles in each lead of this electrocardiogram were marked off into groups of seven, it was found that the second and fourth beats of each of these groups were *a* beats. In tracings taken at other times the *a* beats were less regular in occurrence. More frequently these beats occurred a few times in each lead, sometimes separated by one of the "usual" beats; at other times, an isolated *a* beat

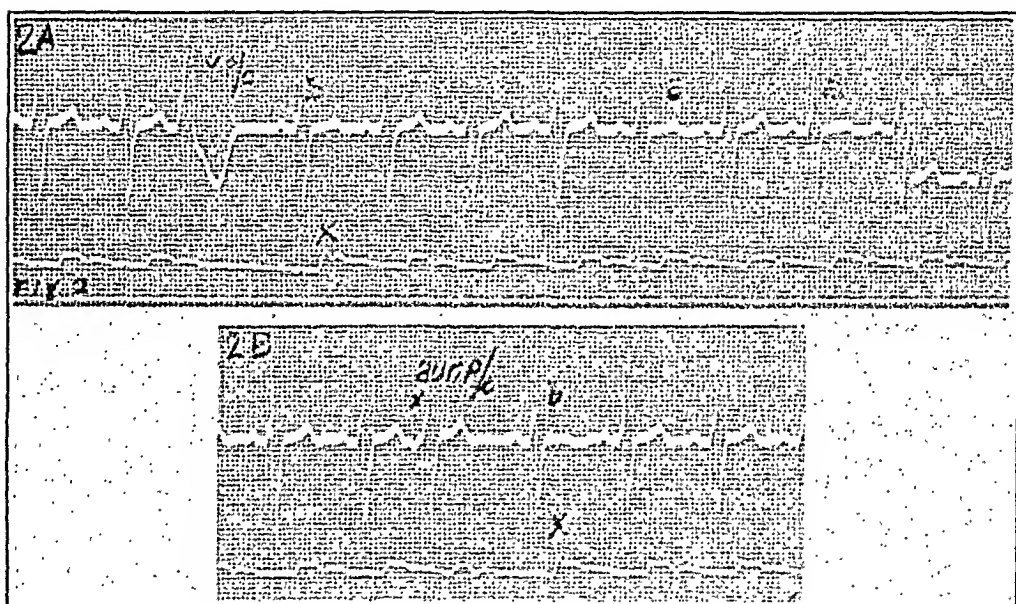


Fig. 2.—Lead II, showing electrocardiogram and brachial arteriogram. A, electrical alternation following ventricular premature contraction and associated large arterial waves; later electrical alternation without arterial wave changes. B, electrical alternation following auricular premature contraction and associated with arterial wave changes.

occurred. Never were two *a* beats found in succession. There was no change in the R-R or P-R intervals, irrespective of the type of cycle. The T-wave changes are not as clearly seen in the first lead as in the second and third leads.

The short QRS conduction time of the *b* cycles, occurring after premature contraction, suggests that an improvement in function may have resulted from the longer rest period (compensatory pause). This might be explained by a greater diastolic filling during the compensatory pause resulting in a larger stroke volume.

The prolongation of intraventricular conduction in the preponderant beats suggests so-called incomplete bundle-branch block. It would seem that a state of balance associated with transient improvement of con-

duction best explains the occurrence of the alternation waves (*a*). The absence of changes in the arteriograms accompanying these *a* beats and the occurrence with the *b* beats is difficult to understand—unless it is considered that the additional rest (compensatory pause) permits generation of greater mechanical force by the *b* beats (larger stroke volume). Our tracings are in many respects similar to ones obtained by Carter and Faulkner in their work on the suspended terrapin heart. In their experiments, the hearts were exposed to severe conditions never encountered in the living animal. They found alternating changes in intraventricular conduction and T-wave voltage. Dr. Harold E. B. Pardee was kind enough to review the electrocardiograms of this patient. He felt that the changes in QRS and T were due to functional variation in a portion of the heart muscles, resulting from what might be called a state of balance easily influenced by minor factors.

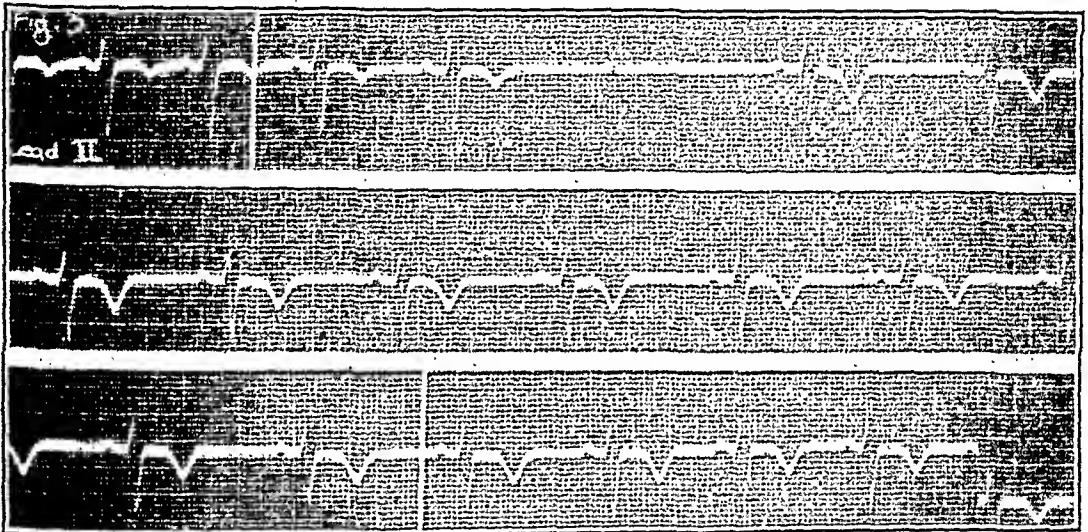


Fig. 3.—Lead II. Continuous strip of record showing the effect produced on the electrocardiogram by pressure on the left carotid sinus. Signals indicate application and removal of pressure. There is shown ventricular standstill for about 2.2 seconds, associated with a sudden drop in rate from 83 to 45 beats per minute, an increase of P-R from 0.16 to 0.20 second and T-wave changes. An abrupt drop of blood pressure occurred from 165/90 to 106/80.

We also took combined records showing the electrocardiogram and respiratory excursions and could demonstrate no relationship between the appearance of electrical alternation and the respiratory cycle. Nor did the administration of atropine or epinephrine affect the appearance of the electrical alternation. The absence of alternation in chest leads (front to back of chest) and the slight difference between the three types of complexes found in the conventional leads suggest that only a small area of the myocardium is involved. Pressure over either carotid sinus did not produce electrical alternation. Atropine abolished the carotid reflex; epinephrine did not.

In our attempt to ascertain the cause of his convulsions, we have considered ventricular standstill (Adams-Stokes syndrome), paroxysmal auricular or ventricular tachycardia, paroxysmal auricular or ventrien-

lar fibrillation, idiopathic epilepsy, brain tumor, and cerebral arteriosclerosis. Spontaneous hypoglycemia was ruled out by blood sugar studies. Idiopathic epilepsy usually occurs in the earlier decades. The lack of progression and absence of localizing signs since onset of symptoms three and one-half years before would seem to be evidence against a cerebral neoplasm. Esecamilla¹⁹ described the history of a patient who had convulsions quite similar to our patient's in whom he was able to demonstrate the etiology due to transient attacks of ventricular fibrillation. This, of course, is a very rare finding. Some other type of paroxysmal arrhythmia may be the cause of the syncope and convulsions in our patient, but we have not felt able to make a complete differential diagnosis.

We have also considered the possibility of explaining his syncope and convulsions on the basis of an increased activity of the carotid sinus reflex. It is of interest that the application of pressure over either carotid sinus produced the symptoms of blurring of vision, ear noises, vertigo, and marked facial pallor when the test was applied with the patient sitting. The symptoms were not noted when pressure was applied with the patient recumbent. It is possible that the application of carotid sinus pressure with the patient in the standing position might have produced more marked symptoms, but we were reluctant to assume the responsibility of possible injury to him. He was unable to induce the reflex by moving his neck briskly in various positions while standing.

Weiss and Baker¹⁷ have attempted to explain the occurrence of convulsions, vertigo, and syncope on the basis of an overactive carotid sinus reflex. That this may be the explanation of our patient's symptoms is suggested, but not proved, by the electrocardiogram (see Fig. 3). In this tracing is seen a period of ventricular standstill lasting 2.2 seconds and an abrupt slowing of the rate from 83 to about 45 beats per minute. Simultaneous with these changes there occurred a drop of the blood pressure from 165/90 to 106/80.

REVIEW OF THE LITERATURE

Various types of electrical alternation have been described, one of the rarest being alternation of the P-wave alone as described by Chini,⁴ Condorelli^{8, 12} and also by Lewis.² T-wave alternation alone or with changes in the QRS complexes is more frequently encountered. Kapff¹³ among others has described post-extrasystolic alternation in the height of the T-waves. The QRS complexes may be affected alone by this phenomenon and in this type of wave R is more often involved; variations in the S-wave are even more rare.⁵ Alternation in height of the QRS complexes is occasionally found in hearts which have beaten rapidly (fatigue phenomenon of Winterburg).

Instances of modification of the entire QRS complex have been described in man by Condorelli^{8, 12} in auricular fibrillation and by Galla-

vardin⁶ and Smith⁷ during ventricular tachycardia. Here the complexes at times regularly alternated in direction and shape. These last are probably not true examples of alternation but seem to represent premature contractions arising from different foci.

For an extremely comprehensive review of the literature on the subject, as well as a discussion of current theories concerning the phenomena, one should refer to the paper of Laubry and Poumailloux⁹ and the recent monograph by Bruno Kisch.¹⁸

Experimental Work.—Condorelli found isolated alternation of R when he pinched the lower part of the sulcus terminalis of the rabbit and in another rabbit when he tied the collateral branch of the left descending coronary artery. Mines³ appears to have been the first one to demonstrate electrical alternation without mechanical alternation. De Boer,¹⁰ working on the frog heart, showed a number of simultaneous mechanical and electrical tracings in which the small T-waves corresponded with the large ventricular wave. Hering¹¹ found the large T-waves and large R-waves coincident. Condorelli¹² showed more often discordance between the heights of peaks R and T. De Meyer studied the electrocardiographic variations of the T-waves, which he considered an expression of small disturbances of systolic expulsion. Lewis,² in attempting to correlate experimental with clinical observations, felt that alternation in strength of the auricular contraction caused a corresponding variation in the ventricular contractions.

Otto¹⁴ encountered variations of the T-wave when the aorta or the pulmonary artery was compressed suddenly, causing variations in the intracardiac pressure. Henrijean¹⁵ experimentally demonstrated that the T-wave increased in proportion as the contraction diminished. In fact, when the heart was stopped, the greatest T-waves appeared while the electrocardiogram continued to be produced. If the contraction of the heart was brought about by massage, the T-waves decreased as the contraction increased.

Carter and Faulkner,¹⁶ working on the suspended terrapin heart, demonstrated in the presence of mechanical alternation that there might be a great variability in the rate of spread of the excitation wave. They also showed that the speed of intraventricular conduction diminished as the muscle became exhausted. Distinct alternation of the intraventricular transmission interval was found in one of these experiments and seemed related to the degree of mechanical alternation.

SUMMARY

We have presented an unusual case demonstrating electrical alternation of the QRST complexes of the electrocardiogram without alternation of the pulse in a patient who had occasional attacks of syncope and convulsions. An active carotid sinus reflex was present and may have been a factor in producing his symptoms. Two types of unusual beats

were encountered. These were identical in the electrocardiogram, but those following auricular or ventricular premature contractions were associated with large waves in the arteriograms; those occurring in the absence of premature contractions were not associated with changes in the arteriogram. The patient has shown clinical improvement during a period of three and a half years of observation.

We wish to express thanks to Dr. W. A. Sawyer, medical director of the Eastman Kodak Company, for the opportunity for making these studies and also to Dr. J. M. Faulkner and Dr. H. E. B. Pardee for examining the electrocardiograms and for their helpful interest.

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Department of Clinical Reports

SYNCOPE ATTACKS DUE TO A CONGENITAL ANOMALY OF THE RIGHT COMMON CAROTID ARTERY*

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OBSTRUCTION of the carotid artery may result from operative ligation, from aneurysm or arteriosclerosis, or from congenital anomaly—ligation and aneurysm being by far the most common causes of such obstruction. In spite of the efficient design of the arterial circle of Willis, cerebral anemia or infarction may result. The usual symptom produced is contralateral hemiplegia. Marked mental deterioration, syncopal attacks, epileptiform convulsions, and unilateral visual changes have been described. Neurological manifestations following ligation or aneurysm have been described by Todd¹³ (1835), Hare and Holder⁷ (1899), Shikare¹² (1921), Crawford⁴ (1921), Courbon³ (1926), Kampmeier and Neumann¹⁰ (1930), Cohen and Davie² (1933), Dorrance⁶ (1934), and others. Cases of arteriosclerotic obstruction of carotid vessels with resultant cerebral symptoms were reported by Broadbent¹ in 1875, Hunt⁹ in 1914, and Moniz¹¹ in 1930. Congenital anomalies of the carotid artery of any significance are rarely reported in adults; two cases were reported in 1921, one by De Meyer,⁵ and the other by Homans.⁸

The only case like ours, however, which we have found in the available literature is that reported by De Meyer. He described the case of a young man who, at the age of thirty-two years, began having syncopal attacks, ataxia, and profound asthenia; he became confused and his mental powers deteriorated. On physical examination the right common carotid artery was found to be greatly narrowed and the heart was in a median position.

REPORT OF CASE

The patient in our case was a country school teacher and farmer, fifty-two years of age, who came to the clinic complaining of dyspnea, fainting spells, and weakness. He stated that a physician had heard a heart murmur twenty-two years previously and that in the last five or six years the dyspnea on exertion had increased to a pronounced degree. Since about the age of thirty he had experienced frequent syncopal attacks. These attacks had always followed some unusually violent exertion, especially when such exertion was accompanied by excitement. The first attack he could recall had occurred after he had run to avoid a storm. He had reached the house and had sat down, when suddenly everything had turned black;

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his wife had helped him outdoors to get air. On another occasion he had been burning leaves and the fire had nearly got out of control; while violently attempting to pound it out with a stick, he had suddenly found himself lying face down on the ground with his mouth partly full of dirt. At another time an old friend had come to visit him, and as he had rushed quickly to greet him things had turned black, and he had fallen to the floor.

Although as a young man he had prided himself on his endurance and athletic ability, especially in running, he had later become known locally as a man who had "fits" when he exercised. As he grew older, these attacks had been induced more easily, but he had never had an attack except in connection with some unusual exertion. He had usually been able to tell when an attack was coming on; he would experience a strangling sensation in his throat, fight for breath, and perhaps call for help, and he would then become pale or cyanotic and fall in a brief faint. He would regain consciousness in a few seconds or few minutes. Witnesses had never observed muscular spasm; he had not been incontinent of urine and had never bitten his tongue.

While the patient was under observation in the hospital an attack came on after he had walked rapidly up and down the corridor. He suddenly turned white, sat down, and began to yell at the top of his voice. This continued for about two minutes. It was difficult to examine him at the time because of the commotion he created. His pupils were somewhat dilated; his extremities and face were quite cold; and perspiration was rather marked.

On physical examination the patient was found to be obese, and he looked considerably older than the stated age of fifty-two years. His blood pressure was 134 systolic and 78 diastolic; the pulse was totally irregular (auricular fibrillation), the rate being 80 beats per minute. Pulsation in the right common carotid artery was very feeble, whereas that in the left common carotid artery was normal. The radial pulses were equal. Expansion of the thorax was somewhat limited. The heart was markedly enlarged to percussion, the left border extending to the mid-axillary line. A systolic murmur could be heard over the whole precordium, but was loudest at the apex. The second pulmonic sound was somewhat accentuated. There were a few moist râles at the bases of both lungs. Otherwise, physical examination gave essentially negative results.

Vision in the right eye was 6/7, with correction, and in the left eye 6/12, with correction. The pupils were large; the reflexes were slow; and the fields were roughly normal. Fundoscopic examination revealed very little retinal arteriosclerosis. At rest, there was a slight arterial pulsation visible in the left retinal arteries. No pulsations were seen in the right eye. After exercise arterial pulsation became very marked in the left eye, but none was noted in the right eye. When the patient lay down, pulsations in the left eye were no longer visible. Changes in posture caused only slight changes in blood pressure. Urinalysis and examination of the blood, including the Kahn and Kline tests, gave negative results. Roentgenograms of the thorax disclosed nothing of significance, except the rather marked cardiac enlargement. The electrocardiogram showed a rate of 68 beats per minute, and auricular fibrillation with ventricular premature contractions, slurring of the QRS complex in Lead I, notched QRS in Leads II and III (QRS 0.10, 0.12, 0.12 seconds), and inverted T-waves in Leads II and III.

While under our observation the patient on several occasions became disoriented; his memory was very defective; he was quite garrulous; and he gave evidence of a serious degree of mental deterioration. Neurological examination gave no evidence of lesions in the central nervous system, and our opinion was substantiated that the cerebral anemia resulting from carotid inadequacy could best explain both the

mental symptoms and the attacks of syncope. A congenital defect of the right common carotid artery, perhaps associated with insufficient collateral connections through the circle of Willis, seemed to be the best explanation for these observations.

This case is of unusual interest for several reasons, one of which is our inability to find more than one other like it in the available literature. We believe that this patient undoubtedly has a congenitally underdeveloped right common carotid artery, and consequently an inadequate supply of blood to his brain. The probabilities are that he may also have some congenital defect of the communicating branches between the right and left sides at the base of the brain. We believe that his symptoms of cardiac insufficiency are attributable to two factors: (1) an old mitral endocarditis with probable stenosis, although the physical findings are not typical for this, and (2) obesity. We have no other adequate explanation to offer for the symptoms of cardiac insufficiency.

It is interesting to speculate upon why the patient's attacks began at the age of thirty years and not before. There is, we believe, at least a partial explanation for this. His weight had increased considerably, within a relatively short period, from 164 to 185 pounds (74 to 84 kg.). Because of the old mitral endocarditis, his cardiac reserve was probably not as great as it had been when he was younger, so that, with the inadequate common carotid artery on the right side, he was not able to maintain an adequate supply of blood to his brain during strenuous exercise. Other evidence that would seem to support this is that, as he became older and as the cardiac reserve continued to decrease, the attacks were more easily precipitated. We believe the mechanics responsible for this patient's symptoms are practically the same as those that are present in aortic stenosis. He did not have a hypersensitive carotid sinus.

The features to which De Meyer called attention in his case were the disorientation and confusion. These same features were present in our case and had become pronounced during the few months before we saw the patient. This was probably the result of the inadequate supply of blood to the brain, together with some sclerosis of the arteries of the central nervous system. We believe that if patients have attacks of unconsciousness, or syncope, and no adequate cause can be found, some congenital defect of the large vessels of the neck should be sought for as the cause.

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COMPLETE HEART-BLOCK IN HYPERTHYROIDISM*

REPORT OF A CASE

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ALTHOUGH disturbances in cardiac mechanism are frequently associated with hyperthyroidism, heart-block is rarely seen in this condition. Davis and Smith¹ have recorded six cases of heart-block in hyperthyroidism, but all of these followed acute infections. In a careful review of the literature they were able to find four similar instances. In the case reported here, however, it is believed that the heart-block has resulted from hyperthyroidism itself rather than from infection.

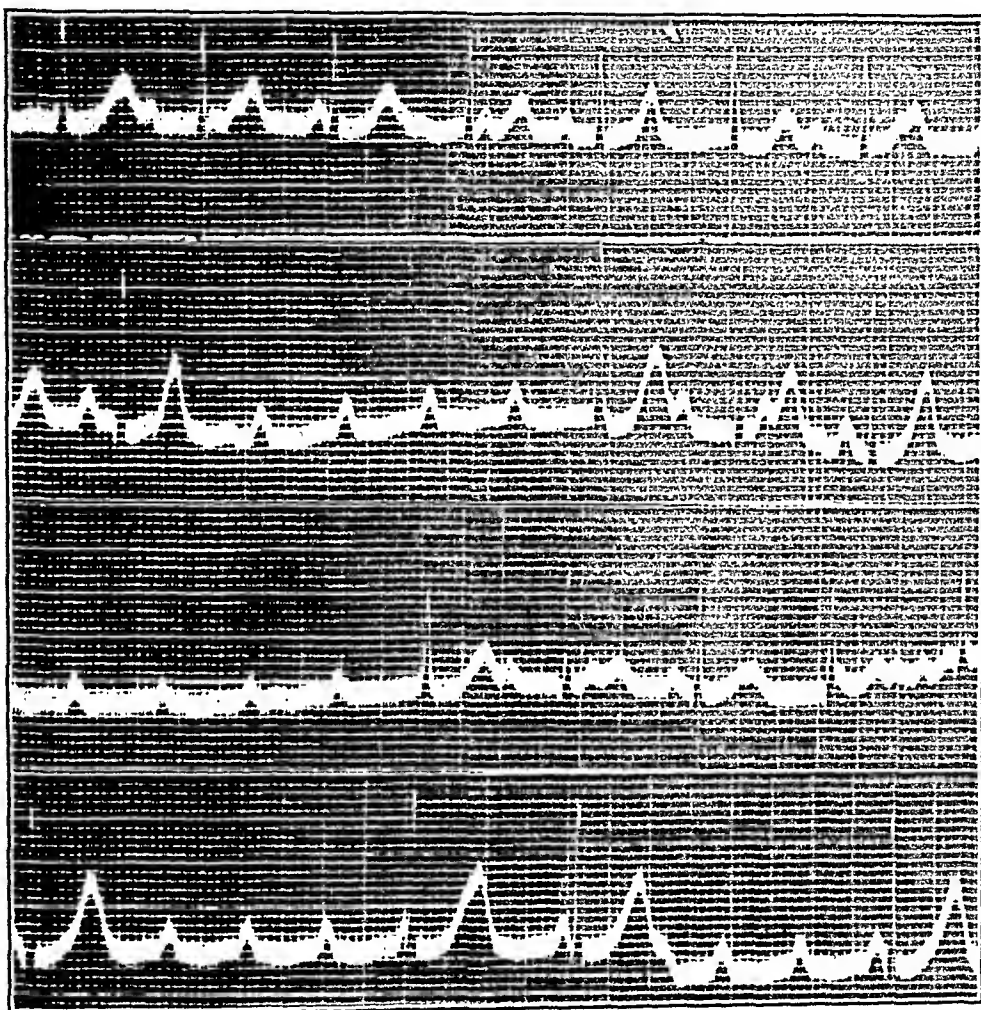


Fig. 1.—Usual four leads. Electrocardiogram taken July 4, 1935, showing complete heart-block.

CASE REPORT

A white housewife, thirty-nine years old, was admitted to the University Hospitals, July 4, 1935. While on a picnic she suddenly fainted. After a few moments she regained consciousness only to faint again shortly thereafter. This process

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recurred about fifty times during the day. On further questioning it was learned that she had had attacks of palpitation for about one year and had been "nervous" and subject to fatigue during this time. She had lost about twenty pounds, some of which, however, she regained. The history otherwise was of no significance.

On examination she was found to be a well-developed, well-nourished woman. The skin was moist. The thyroid gland was enlarged and adenomatous. The apex rate ranged from 60 to 70 beats per minute with rather long pauses of asystole at intervals. Isolated auricular beats could be heard, and auricular venous waves in the neck could be seen which were not associated with ventricular beats. Blood pressure was 130/80. Palpation over the precordium revealed no abnormalities. The heart borders were within normal limits. No murmurs were heard; lungs normal; no râles at bases; abdomen normal; no enlargement of liver or spleen; no edema. Admission temperature 38° C.

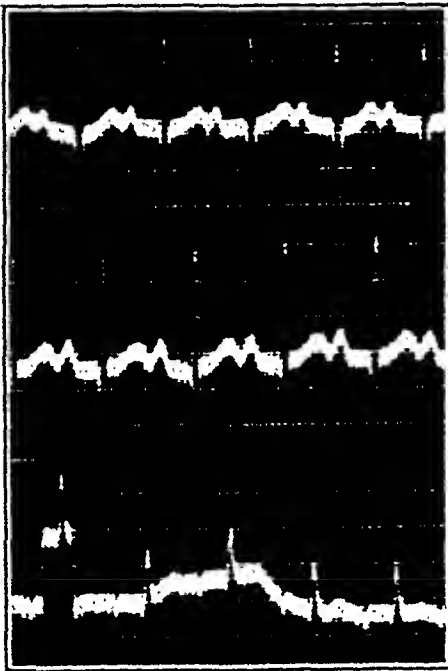


Fig. 2.

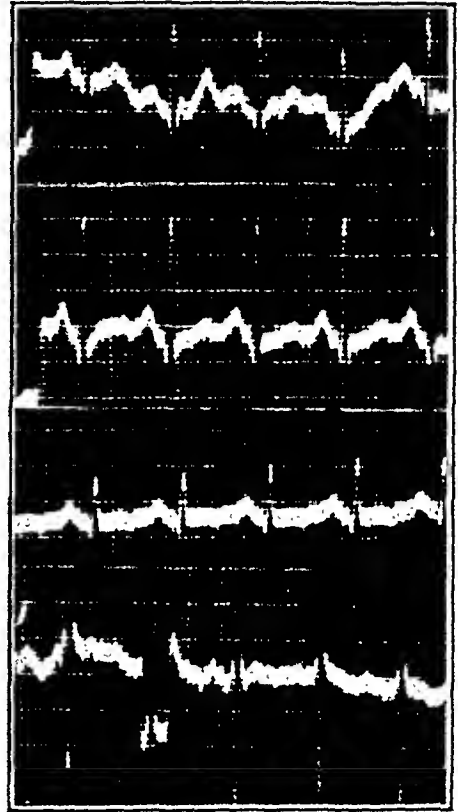


Fig. 3.

Fig. 2.—Usual three leads. Electrocardiogram taken July 10, 1935, showing sinus tachycardia with P-R interval of 0.24 sec. Lugol's solution administered since record shown in Fig. 1 was made.

Fig. 3.—Usual four leads. Electrocardiogram taken July 24, 1935, nine days after thyroidectomy. Shows normal mechanism.

A diagnosis of complete heart-block associated with hyperthyroidism was made. Electrocardiogram (Fig. 1) confirmed the diagnosis of heart-block. The basal metabolic rate on July 5, 1935, was +36 per cent. The white blood count was 8,200, with a normal differential count. Blood Wassermann test was normal. Blood urea nitrogen was 14 mg. and the plasma cholesterol, 106.

COURSE

Soon after admission atropine (1/30 gr.) was given hypodermically and produced no noticeable effect clinically or in the electrocardiogram. This was repeated later with the same result.

Lugol's solution, 5 minims t.i.d., was started July 6. This was increased gradually to reach 20 minims t.i.d. on July 14.

An electrocardiogram taken July 8 after approximately forty-eight hours of iodine therapy showed prolonged A-V conduction with dropped beats.

An electrocardiogram taken July 10 showed sinus tachycardia with P-R interval of 0.24 sec. (Fig. 2).

An electrocardiogram taken July 15 showed normal mechanism. The basal metabolism decreased to +3 per cent on this day, and operation was performed by Dr. C. H. Lenhart the same day. A large adenomatous thyroid was removed.

Lugol's solution was continued postoperatively. The progress was uneventful until July 18, when auricular fibrillation with a ventricular rate of 160 commenced. Digitalis was withheld as long as thought advisable, but finally 1½ grains were given because of the gravity of her condition. A similar dose was repeated in six hours after which the fibrillation ceased. A normal mechanism has continued since that time. (Fig. 3 shows electrocardiogram taken July 24.) She was last seen March 1, 1936, and was in excellent health.

DISCUSSION

Although the admission temperature of 38° C. was maintained for forty-eight hours, we do not believe that infection played any part in the production of the block. There was no leucocytosis and no evidence of infection on examination. The prompt response to Lugol's solution indicates that the block was a part of the thyroid toxicosis.

SUMMARY

A case of hyperthyroidism associated with heart-block is reported. The block disappeared under iodine therapy and did not recur after removal of the adenomatous thyroid.

The author acknowledges appreciation to Dr. R. W. Scott for his assistance in this case.

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A CASE OF ACQUIRED INTERVENTRICULAR SEPTAL DEFECT ASSOCIATED WITH LONG-STANDING CONGESTIVE HEART FAILURE*

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INTERVENTRICULAR septal defect is commonly a congenital lesion. The unusual cases of acquired septal disease are of necessity the result of a destructive process and may be divided into two types: (a) those due to bacterial endocarditis or a pyemic metastatic abscess and (b) those following an acute coronary vessel closure. Though rupture of the heart following an acute coronary closure is quite common, the septum usually escapes rupture on account of the extensive collateral circulation.

Reports of cases of rupture of the septum, associated with acute or chronic coronary vessel closure, have appeared in the literature from time to time. Additional instances have recently been added by Freeman and Griffin,¹ Kepler, Berkman, and Barnes,² and Sager.³

The following case is of interest in that the patient was known to have had coronary artery disease for some time, associated with an acquired healed septal defect which, from the type of lesion and healing, must necessarily have been of long duration. Despite this large defect he survived long enough to develop chronic congestive failure, which for a considerable period responded to the usual diuretic measures.

REPORT OF CASE

H. R., No. 19294, aged fifty-seven years, was admitted to the Montefiore Hospital on July 25, 1930, with a history of weakness, shortness of breath, and swelling of the legs and abdomen. He was known to have had hypertension for three years. On Sept. 2, 1929, after a restless night, he suddenly became unconscious, was cyanotic, had stertorous breathing, and blood trickled from his mouth. Unconsciousness lasted one and one-half hours and was followed by marked weakness, with which he was confined to bed. One month later he had a similar attack; altogether he had five such episodes, the last one occurring in December, 1930. Following his last seizure he had dyspnea on slight exertion, a diminished urinary output, and swelling of the legs and abdomen. Salyrgan had to be administered, and one week prior to admission to the hospital it was necessary to perform a paracentesis of the abdomen. He had received morphine for several months and had become addicted to its use.

Examination showed a fairly well-nourished, well-preserved, middle-aged man lying comfortably in bed. His lips were slightly cyanotic. The pupils were equal and constricted (morphine); the fundi showed marked sclerosis of the retinal vessels, with narrow irregular constricted arteries and arteriovenous constrictions. There was considerable dilatation of the veins of the neck in the upright position. The

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pulsations of the carotid arteries were visible bilaterally. The chest was of the emphysematous type, and there was bilateral effusion in the pleural cavities. The apical impulse was palpated at the fifth intercostal space just below the nipple line. A fine systolic thrill was palpable over this region, and a questionable presystolic apical murmur was heard. There was a prolonged systolic murmur audible over the entire precordium and base of the heart. It was louder at the apical region and in the ensiform area. The apical second sound was sharp and almost clicking, the pulmonic second sound greatly accentuated. The heart rhythm was regular. The blood pressure was 184/128. The radial arteries were moderately sclerotic, the pulses full and bounding.

X-ray examination of the chest showed bilateral hydrothorax, marked enlargement of the heart, the left border reaching almost to the left lateral wall. The electrocardiogram showed slurring of complexes and right axis deviation.

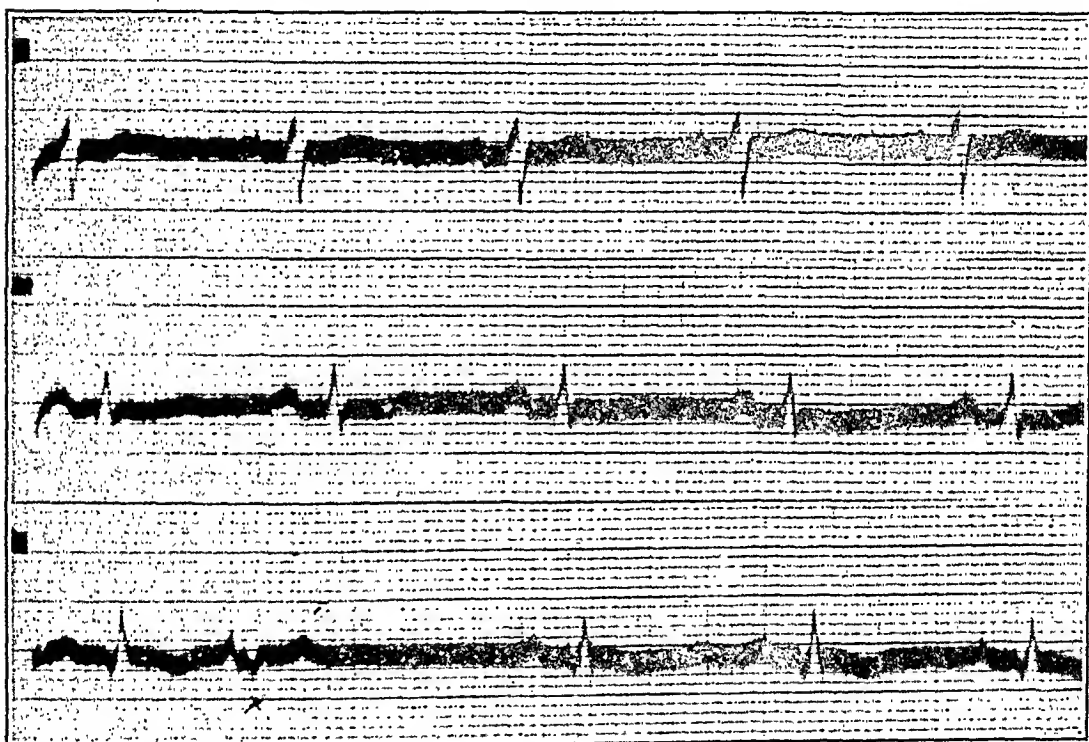


Fig. 1.—Electrocardiogram showed slurring of QRS. complexes, right axis deviation, and one aberrant ventricular complex.

The abdomen was large and flabby, and there were shifting dullness and flaring of the flanks. The liver edge was four fingerbreadths below the costal margin, firm, regular, and tender. There was slight dependent edema extending to the sacrum.

Course and Progress.—He improved greatly on massive doses of urea (69 gm. daily) and salyrgan and lost most of his edema. He continued to bring up bloody sputum occasionally. Despite diuretic therapy, congestive heart failure and ascites recurred, and paracentesis of the abdomen had to be performed repeatedly, with removal of from 2,500 to 3,500 c.c. of a slightly turbid, amber-colored fluid. On Jan. 14, 1931, he suddenly vomited considerable dark brown, sour-smelling fluid containing food particles, and became irrational and incoherent. Examination of the chest at this time showed dullness at both bases, with bronchovesicular breath sounds and coarse râles. He subsequently improved, but on Feb. 7, 1931, he had slight swelling of the submaxillary lymph nodes, a rise in temperature, and a blood count of 20,000 white cells, with 86 per cent polymuclear cells. The next day there were

signs of massive consolidation at the left base, in addition to the hydrothorax, a rise in the temperature to 101° F., a rapid pulse, cyanosis, and a respiratory rate of 32 per minute, attributed to lobar pneumonia. Thoracentesis of the left chest yielded 200 c.c. of serosanguineous fluid. He was put in an oxygen tent but died that evening.

Necropsy.—Only the findings referable to the heart are reported.

Measurements: Tricuspid ring	13 cm.
Pulmonic ring	7.5 cm.
Aortic ring	7 cm.
Mitral ring	11 cm.
Left ventricular wall	18 mm.
Left ventricular wall	3 mm. at apex
Right ventricular wall	8 mm.



Fig. 2.—Gross picture of heart showing generalized cardiac hypertrophy and marked thinning of apex and replacement fibrosis. Entire lower half of septum shows replacement fibrosis and septal defect in middle of this area.

Pericardial surfaces were smooth and glistening, except for a patch of thickened grayish visceral pericardium over the apex. The heart was uniformly enlarged, and somewhat apple shaped. The right auricle was markedly dilated, and the musculi pectinati were considerably hypertrophied. There was a considerable amount of hypertrophy of the myocardium of the right ventricle and dilatation of the chamber. The tricuspid ring was markedly dilated. The left auricle was considerably dilated, and there was a definite subendocardial fibrosis of the mural endocardium. The mitral valve showed no abnormalities. The left ventricle was slightly hypertrophied and considerably dilated. Papillary muscles were considerably hypertrophied. The apex was thinned out, and the myocardium was replaced by fibrous tissue. The endocardium in this region was thickened and gray. Likewise the entire lower half of the septal wall showed replacement of the myocardium by fibrous tissue with marked narrowing of the endocardium. In the central portion of this area of

fibrosis of the septum was a circular defect, measuring several centimeters in diameter, whose edges were round, regular, and very smooth. This defect when viewed from the right ventricle revealed a large communication between the left and right ventricles. A portion of the right ventricle adjacent to the area of septal fibrosis showed thickened endocardium and small areas of fibrosis. Right coronary artery showed considerable atherosclerosis with calcification and dilatation of the lumen. No areas of narrowing were encountered. The left anterior descending coronary divided into a large deep and a smaller superficial branch about 1 cm. from the origin of the left coronary artery. About 1 cm. from this division a small superficial branch was completely occluded by a yellowish calcific plaque. The deeper branch showed severe atherosclerosis and calcification with frequent narrowing of the lumen by large yellowish gray plaques. The first lateral branch of the left circumflex was completely occluded about 1 cm. from its origin by a reddish firm thrombus. Distally the same artery was completely occluded by a yellowish calcific plaque. Several terminal lateral branches of the left circumflex also showed marked narrowing or complete occlusion by yellowish plaques.

DISCUSSION

The acquired cases of interventricular septal perforation recorded in the literature have chiefly been incidental to coronary artery disease. The course and duration have usually been short, never exceeding ten days. Our case is noteworthy in that, while secondary to severe coronary disease, the defect was healed, large, and smooth, and the patient lived for a long time during which he developed advanced congestive heart failure, which responded to diuretic therapy. It would not be reasonable to conjecture the existence of an independent congenital septal defect with independent coronary disease and myocardial infarction. Both the transverse and descending branches of the left, as well as the right, coronary arteries were markedly involved. The myocardium of the septum up to and including the perforated area was a mass of fibrotic tissue. It is difficult to assume that infarction and fibrosis extended to an area contiguous with a congenital septal defect without sparing an intervening area of normal myocardium between infarcted area and patent septum. The ring around the defect was irregularly sclerotic, the adjacent myocardium extensively scarred, with virtually no remaining muscle tissue left. It is reasonable to assume that an individual with so large a congenital septal defect would not have survived to old age to develop myocardial infarction.

It has been well established that the cases of septal perforation following coronary disease show extensive involvement of both coronary arteries. The richly anastomotic circulation in the septum becomes inadequate so that it is involved as part of the myocardial infarction. Subsequently, with weakening of the wall from alterations in blood pressure, ventricular aneurysm and rupture may occur. Violent effort may be a deciding factor in an already weakened wall in producing perforation.

The diagnosis should offer no great clinical difficulty. In a known case of coronary artery disease, a murmur appearing in the fourth and

fifth left interspaces and over the precordium, as in the common type of interventricular defect, should lead to the correct diagnosis. The presence or absence of a thrill and its intensity depend upon the size of the defect, being louder with smaller ostia. In this case, the presence of a presystolic apical rumble, systolic apical thrill, and marked accentuation of the pulmonic second sound, led to a diagnosis of a rheumatic mitral stenosis. There was, however, a prolonged systolic murmur of unusual intensity over the entire precordium and base, loudest at the ensiform area and apex, as in typical congenital septal defect. It was thought difficult to correlate the location and intensity of the murmur with simple coronary disease. A murmur suggestive of a congenital interventricular septal lesion in a known case of coronary disease justifies labeling the septal defect as an acquired one.

SUMMARY

An additional instance of an acquired interventricular septal defect secondary to coronary disease is reported. The case is noteworthy in that the individual, despite coronary artery and septal disease, lived long enough to develop chronic congestive heart failure, which for a considerable period was amenable to the usual diuretic measures.

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Department of Reviews and Abstracts

Selected Abstracts

Robb, Jane Sands, and Robb, Robert Cummings: The Excitatory Process in the Mammalian Ventricle. *Am. J. Physiol.* 115: 43, 1936.

Simultaneous direct and indirect leads have been recorded from mammalian hearts on a multigalvanometer set-up in which the three galvanometers were connected through resistance to a central terminal.

A standard Lead II could therefore be accurately compared with any two points on the surface of the heart without introducing error of time or potential of the direct electrodes.

When times of initial negativity are read from tracings obtained by placing the direct electrodes along the axis of given muscle bundles, these times on the superficial sinospiral and superficial bulbospiral muscles are found to increase in an orderly manner from apex to base.

Data are cited from literature which could also be interpreted as showing progressive delay in activity along the superficial sinospiral muscle.

Conduction rates calculated from point to point along a muscle strand give a mean value of 2375 ± 128 mm. per second.

Conduction rates for the dog and monkey (*Macacus rhesus*) are not statistically distinguishable.

If any two direct contacts along a given muscle band are separated by a cut, there occurs a delay in the arrival of the intrinsic wave at the contact farthest from the apex. If the whole cross-section of the muscle is involved, the intrinsic wave disappears from the contact farthest from the apex.

Evidence is presented that the wave of excitation does cross the interventricular groove.

These observations cannot be explained according to the present theory of conduction of the excitatory process in the ventricle, i.e., the "radial penetration" theory of Lewis.

These data indicate that the excitatory process is conducted "axillary" in the muscles studied along a pathway parallel to fiber direction.

AUTHOR.

Green, Harold D.: The Coronary Blood Flow in Aortic Stenosis, in Aortic Insufficiency and in Arterio-Venous Fistula. *Am. J. Physiol.* 115: 94, 1936.

Since circulatory abnormalities such as aortic insufficiency, aortic stenosis and arteriovenous fistula produce striking changes in the heart and circulation and occasionally myocardial injury, knowledge of their effects on coronary circulation has considerable clinical and physiological significance. The effects of these abnormalities on coronary circulation have therefore been studied in the dog by a slight modification of the method previously reported by Green, Gregg, and Wiggers.

These studies revealed that under the conditions of these experiments (1) lesions of the type of uncompensated aortic insufficiency and arteriovenous fistula cause a decrease in coronary flow chiefly during diastole, by lowering aortic diastolic pressure; (2) this decreased flow is, to a considerable extent, mitigated by a concomitant

increase in the coronary flow during systole resulting from a relative lowering of the systolic peripheral coronary resistance in relation to aortic pressure; (3) in these lesions, compensation through peripheral vascular constriction, sufficient to restore a normal mean blood pressure, may increase coronary flow to or even above normal because the systolic peripheral coronary resistance is elevated relatively less than the aortic pressure; and (4) lesions such as aortic stenosis decrease coronary flow mainly during systole by causing a relatively higher degree of systolic peripheral coronary resistance in relation to aortic pressure.

The question is raised whether an increased flow, such as that obtained by compensation during aortic insufficiency, is commensurate with the increased work of the heart.

It is concluded that the increased systolic peripheral coronary resistance in aortic stenosis is caused by the abnormal height of intraventricular systolic pressure compared with aortic systolic pressure. Some of the factors considered in the attempt to explain the other changes of peripheral resistance observed are that the diastolic size of the ventricle and the wide pulse pressure operate in some manner to alter the extravascular constriction of the vessels and that reflex or metabolic action may cause changes in vascular size. It is considered impossible, however, at the present time to arrive at any definite conclusions.

AUTHOR.

Scott, John C.: *The Cardiac Output in the Standing Position.* *Am. J. Physiol.* 115: 268, 1936.

The cardiac output of a single individual has been observed in the recumbent, sitting, and standing positions. During the winter season in the standing position high A-V differences are usually associated with high oxygen consumption; in the summer this relationship is reversed. The average standing cardiac output is lower than that of the recumbent or sitting positions. The output is influenced by various undefined environmental factors under so-called basal conditions, particularly if the subject is standing.

AUTHOR.

Read, J. Marion, and Barnett, Charles W.: *New Formulas for Predicting Basal Metabolic Rate from Pulse Rate and Pulse Pressure.* *Arch. Int. Med.* 57: 521, 1936.

A new method for the derivation of formulas for predicting the basal metabolic rate from pulse rate and pulse pressure is reported.

The accuracy of the new formulas is compared with that of certain former ones.

The inaccuracy of the determination of basal metabolism by indirect calorimetry is pointed out.

The accuracy of the new formulas is shown to compare favorably with the accuracy of clinical calorimetry.

These formulas are valuable (1) for estimating the basal metabolic rate if the facilities for measuring the consumption of oxygen are not available and (2) for checking the reliability of the metabolic rate as determined by indirect calorimetry. If there is a marked disparity between the results obtained by the two methods, the test should be repeated. In many cases the metabolic rate predicted by the pulse rate and pulse pressure obtained in the morning before the patient arises may be more accurate than the rate determined by measuring the consumption of oxygen after the patient has arisen, dressed, and traveled to a laboratory.

AUTHOR.

Orgain, Edward S., Wolff, Louis, and White, Paul D.: Uncomplicated Auricular Fibrillation and Auricular Flutter: Frequent Occurrence and Good Prognosis in Patients Without Other Evidence of Cardiac Disease. *Arch. Int. Med.* 57: 493, 1936.

Paroxysms of auricular fibrillation and of auricular flutter occur not infrequently in persons with no other signs of cardiac disease.

Follow-up studies on 54 patients of the present series (47 with auricular fibrillation alone, 5 with auricular flutter alone, and 2 with both) revealed, after the lapse of a significant number of years, a low mortality rate, little important cardiac disease, and but a single instance of hyperthyroidism.

The prognosis for life and for the maintenance of adequate cardiac function is good.

The outlook for future improvement, manifested by a decrease in frequency or complete cessation of paroxysms, is frequently good.

Thus, auricular fibrillation and auricular flutter are in some persons merely exaggerated functional disorders of the heart, no more indicative of cardiac disease or of a poor prognosis than are premature beats or auricular paroxysmal tachycardia.

AUTHOR.

Holzer, W.: The Transmission of Electric Currents Through Biological Material—Including Comments on the Electrocardiographic Method. *Ztschr. f. Kreislaufforsch.* 28: 113, 1936.

The author develops the theory of recording electrical currents mathematically, taking into account the properties of the biological material containing the current generator, the skin resistance and capacity, and the resistance of the measuring instrument, as well as the vibration frequency of the generated current. Twenty-four determinations on five individuals with Lead II, using silver electrodes, gave a calculated value for the internal resistance of 740 ohms on the average, and a range of 600 to 1,000 ohms. The skin resistance was 2,000 to 16,000 ohms/cm.² (average 8,400 ohms/cm.²); skin capacity was 0.01 to 4 microfarads/cm.² (average 0.36 microfarads). A harmonic analysis of a normal electrocardiogram obtained from averaging 42 curves (Lead II) was made. No vibrations over 200 were present. The author advocates the use of a "direct voltage" amplifier and a cathode ray oscillograph for electrocardiographic registration. The curves so obtained showed the presence of an S-wave and splintering of the R-wave.

L. N. K.

Frey, Leopold: The Relationship Between "Variable Bundle-Branch Block" and Extrasystoles in Malignant Diphtheria. *Ztschr. f. Kreislaufforsch.* 28: 73, 1936.

The author reports two cases in which the electrocardiogram showed complete A-V block, arborization block, and "variable bundle-branch block." The contour of the ventricular extrasystoles which appeared resembled the ventricular complexes of some of the idioventricular beats. The author concludes from this that the two types of beats arose from the same focus.

L. N. K.

Danzer, C. S.: The Diagnostic Significance of Gallop Rhythm. *New York State J. Med.* 36: 10, 1936.

It is pointed out that gallop rhythm generally occurs as a sign of serious myocardial disease of impending or obvious heart failure. Gallop rhythm is probably the most direct sign of heart failure, and perhaps of myocardial disease, especially

when this phenomenon is associated with an increase in the P-R interval or an inversion of the T-waves in the two leads of the electrocardiogram.

Gallop rhythm also occurs occasionally in compensated aortic insufficiency, severe tachycardia, Graves' disease, and with auricular extrasystoles without concurrent heart failure.

PART OF A SYMPOSIUM

on

RHEUMATIC FEVER

at the

Second Annual Meeting of The American Association for the Study and Control of Rheumatic Diseases and the Fourth Conference on Rheumatic Diseases

June 10, 1935

Atlantic City, N. J.

Swift, Homer F.: The Nature of Rheumatic Fever. *J. Lab. & Clin. Med.* 21: 551, 1936.

Rheumatic fever presents protean manifestations, which, when few in number, often make it difficult to distinguish the disease from closely related conditions; hence it is impossible to characterize the malady too accurately. The histopathological picture, while presenting the well-recognized manifestations of inflammation, has certain peculiar features, chief of which are damage to the mesenchymal ground substance by some noxious agent, the nature of which has not been definitely established; this damage is followed by hyperplasia and multiplication of primitive cells that often assume a definite architectural form. Inflammatory features are seen early in the rheumatic lesion in contrast to the initial cellular injury followed by the signs of inflammation usually seen in virus-induced diseases. The tissue of rheumatic patients appears to be unusually vulnerable to several injurious agents, and especially to substances contained in or derived from streptococci. Possibly this state of hypervulnerability, or allergic irritability, makes the tissues susceptible to the action of a hypothetical specific virus; on the other hand, the state of allergic irritability may be the result of prolonged action of such a virus, and the immediate attack may be merely set off by a bacterial infection or other traumatic insult. While much investigation remains to establish firmly and to correlate many of the phenomena discussed, the following working hypothesis remains to guide prophylaxis: It appears advisable to protect the rheumatic subject from certain bacterial infections as well as from other injurious and depressing influences if he is to be spared the repeated attacks of a disease that eventually lead to permanent cardiac disability, for repeated or recurring infections usually exert a more deleterious influence than does the initial attack.

AUTHOR.

Shapiro, M. J.: The Natural History of Childhood Rheumatism in Minnesota. *J. Lab. & Clin. Med.* 21: 564, 1936.

Rheumatic disease in children in Minneapolis is essentially the same as in other centers throughout the world.

Rheumatic fever is more prevalent in Minneapolis in the early spring and late fall. During the summer the disease is at its lowest ebb. Similar curves from other large centers are presented.

Childhood rheumatism occurs most commonly in children between five and six years of age.

This disease is definitely familial. The familial tendency is three times as great in a rheumatic group as in a nonrheumatic group.

Rheumatism in children in a considerable number of instances follows an upper respiratory infection, but most commonly develops slowly with no preceding infectious process.

The great majority of children who complain of leg pains are not suffering from rheumatism. A differential diagnostic table based on clinical observations is presented.

The normal expectancy of recurrences of rheumatism has been determined. This material is to be used as a control in determining the efficacy of any type of specific treatment which might be tried in the future.

An analysis of the findings of thirty-four children who have died is presented.

AUTHOR.

Dawson, M. H., and Tyson, T. Lloyd: The Relationship Between Rheumatic Fever and Rheumatoid Arthritis. *J. Lab. & Clin. Med.* 21: 575, 1936.

The relationship between rheumatic fever and rheumatoid arthritis is, at the present time, of greater theoretical than practical importance. For clinical purposes it is important that the two should be differentiated whenever possible for, in typical cases, each presents its own symptoms, each demands its own therapeutic management, and each requires its own prognosis. For theoretical reasons, however, a clearer understanding of the nature of the relationship of the two diseases is of great importance and may contribute much to our knowledge of both conditions.

Evidence has been presented to show that rheumatic fever and rheumatoid arthritis are intimately related and possible different manifestations of the same pathological process. Of particular significance is the clinical and anatomical evidence obtained from a study of "atypical" and "borderline" cases. The clinical evidence suggests that the two form a continuous sequence of one disease process with different expressions in each individual phase. These different expressions appear to be in large measure determined by the age of the patient, but undoubtedly other factors, such as individual host susceptibility, are also of importance. The pathological evidence, representing a difference in degree rather than in kind, strongly suggests that the two represent different responses to the same, or closely related, etiological agents.

A final understanding of the relationship between rheumatic fever and rheumatoid arthritis will not be possible until the etiology of both diseases has been definitely established. At the present time there is a certain amount of evidence suggesting that infection by *Streptococcus hemolyticus* plays a rôle in the production of both diseases. However, this evidence is as yet far from complete, and, even if it could be established that both diseases were due to the same agent, it would not prove their identity. The situation would then be analogous to that which exists with syphilis and yaws. Here the etiology of both diseases is definitely known, yet the relationship between the two is still a matter of controversy. It is obviously more difficult, with the knowledge at present available, to arrive at a complete understanding of the relationship between rheumatic fever and rheumatoid arthritis.

AUTHOR.

Nichol, E. Sterling: Geographic Distribution of Rheumatic Fever and Rheumatic Heart Disease in the United States. *J. Lab. & Clin. Med.* 21: 588, 1936.

A review of available data indicates that there is a definite inequality in the distribution of rheumatic fever and rheumatic heart disease in the United States, the amount being much less in the southern states. The influence of geographical location on the clinical incidence of rheumatic fever and rheumatic heart disease is emphasized by contrasting the findings in southern Florida and New England. During the past five years, in spite of a careful search for subclinical cases, the admission

rate of rheumatic fever, rheumatic carditis, or chorea in a general hospital in Miami was only one-tenth the rate in Boston during the same period.

Only 1.3 per cent of "cardiac" patients found in Miami both in hospital and office practice had rheumatic heart disease determined clinically to have been acquired during life or residence in the South, as compared with a recent estimate that 31.9 per cent of "cardiac" patients encountered in New England were of rheumatic type.

AUTHOR.

Rinehart, James F.: An Outline of Studies Relating to Vitamin C Deficiency in Rheumatic Fever. J. Lab. & Clin. Med. 21: 597, 1936.

The concept that rheumatic fever may be due to the combined influence of vitamin C deficiency and infection rests upon a broad experimental basis. In guinea pigs, under this dual influence, lesions comparable to those of rheumatic fever may develop in the heart and joints. The not infrequent occurrence of subcutaneous nodules appears to complete the pathological similarity. It is of interest that in the experimental work no sharp line can be drawn between a disease picture resembling rheumatic fever and one characterized by a chronic joint disability with pathological similarities to atrophic (rheumatoid) arthritis. There is much evidence indicating a relationship between the two diseases as seen in man.

Epidemiological data seem to support the thesis advanced. Particular significance is attached to the abnormally high incidence of rheumatic fever in the poor.

Clinical studies in progress have afforded encouraging data but are too few, and the period of observation is too short to afford a basis for judgment.

Rheumatic fever is a disease fundamentally characterized by widespread injury to collagen. Based upon the experimental studies and pathologic anatomy of rheumatic fever, a theory of mechanism of the development of the rheumatic lesion is advanced.

Our knowledge of the metabolism of vitamin C is in the process of development. Capacity to store the vitamin is limited. Fatigue and certain infections may deplete the organic reserve. Factors which might inhibit absorption or utilization of vitamin C are not known. Urinary excretion studies may serve as an index of the immediate "saturation" level but are not a gauge of preexisting deficiency. The possible influence of infection in modifying the storage and excretion or utilization of vitamin C is not known. For these reasons, data based upon urinary excretion must be interpreted with care.

The question of what we may reasonably expect from vitamin C therapy in rheumatic fever is considered in the light of the fundamental pathology of the disease. Even though vitamin C deficiency may contribute to the development of the rheumatic lesion, it is only one factor. Some influence of infection also operates. In view of this and the frequently severe injury accompanying the disease, judgment of the preventive or therapeutic effectiveness of vitamin C administration in rheumatic fever can be based only on prolonged clinical study.

AUTHOR.

Sutton, Lucy Porter, and Dodge, Katharine G.: Fever Therapy in Chorea and in Rheumatic Carditis With and Without Chorea. J. Lab. & Clin. Med. 21: 619, 1936.

Fever, by whatever means produced, is a satisfactory method of treatment of chorea, in that the duration of the attacks is thereby appreciably shortened.

The presence of subacute carditis or of inactive rheumatic heart disease is not a contraindication to the use of fever therapy in treating chorea.

The subsequent uphill course of patients with subacute rheumatic carditis who received fever therapy suggests that fever may be of benefit to such patients. We believe that further investigation is warranted.

AUTHOR.

Schmitt, H.: Experimental Investigation of "Rheumatic Atherosclerosis" (Lipoid Deposits in the Vessel Walls After Allergic Injury). *Virchows Arch. f. path. Anat.* 296: 603, 1936.

The author succeeded in producing marked atherosclerotic changes in rabbits which previously were made sensitive to hog serum by feeding 4.4 grams of cholesterol over a period of two weeks. Nonsensitized rabbits were found to require two to four months and many times as large a dose of cholesterol to cause atherosclerosis. The changes found anatomically were atherosclerosis of the aorta with lipoid deposits and calcification. In one of these cases marked proliferation of the intima with occlusion of the lumen of one of the coronary arteries was found.

A group of rabbits which received the cholesterol at the time they were sensitized to hog serum showed a combination of inflammatory and degenerative changes of the vessel walls (adventitia, media, and intima) and marked atherosclerotic changes.

The author believes that early atherosclerosis, particularly in young subjects and especially in the coronary arteries, probably is the result of previous toxic-inflammatory damage to the vessel walls.

A. V.

Root, Howard F., and Sharkey, Thomas P.: Arteriosclerosis and Hypertension in Diabetes. *Ann. Int. Med.* 9: 873, 1936.

The clinical and post-mortem records of 175 diabetic patients were examined. Fifty-four per cent of the patients had had hypertension, indicated by a systolic pressure exceeding 150 mm. of mercury. Eighty-seven per cent of the patients with hypertension and 74 per cent of the patients without hypertension were obese. Arteriosclerotic lesions were found much more frequently in this group of patients than in a similar group of patients without diabetes. If, however, the diabetes was of short duration, severe arteriosclerosis in the aorta occurred somewhat less than in nondiabetic patients, but if the duration of the diabetes exceeded ten years, coronary disease as a cause of death was four times as frequent in the diabetic as in the nondiabetic control series. When accurate data were available, it was found that in the majority of instances diabetes preceded the appearance of hypertension, which affects diabetic patients much more frequently than nondiabetic patients. Gangrene of an extremity had affected 48 of the 175 diabetic patients. Of this group 32 had had hypertension.

Pathologically, the difference in the arteries of patients with and without diabetes who have had gangrene consists in a marked localized proliferation of the intima with deposition of the fatty material including cholesterol crystals in the arteries of diabetic patients.

The authors believe that the premature and excessive development of vascular disease occurs predominantly in muscular arteries under the physical strain, especially in obese patients, and is due to the metabolic changes of diabetes. Hypertension is an important contributing factor in the clinical course of diabetes because it imposes additional strain, even when the patient has lost his obesity, and accentuates greatly the vascular changes in coronary and leg arteries.

E. A.

Clares, Fernando Lopez: Arterial Pressure in Mexican Children. *Arch. latino am. de cardiol. y hemat.* 5: 235, 1935.

Children's blood pressure was taken with the kymometer of Baquez, Gley, and Gomez, using also the oscillatory method from birth up to the age of four months and a combined oscillatory and auscultatory method from the age of four months up to fourteen years; averages for the systolic and diastolic pressures were taken

with the auscultatory method, and averages for the medium pressure with the oscillatory method, taking into consideration the differences between the methods and using cuffs of the following sizes: 4.5 by 14.5 cm., 6 by 19 cm., 1 by 28.5 cm., and the one used on adults, putting the cuff on the left arm.

During the first fifteen days the blood pressure has alternatives increasing and decreasing in both sexes, beginning with the following pressures: newborn infants, systolic 70, medium 60, diastolic 50. The average on the sixteenth day, systolic 77, medium 65, and diastolic 55 in boys, and systolic 75, medium 63, and diastolic 50 in girls. It was noted that blood pressure increases rapidly during the first twelve months in close relation to body strain and weight, being the physiological constant of systolic 85, medium 68, and diastolic 55 in boys and systolic 82, medium 68, and diastolic 51 in girls.

During puberty the blood pressure is higher in girls from twelve to fourteen years old than it is in boys. The blood pressure is lower in premature infants than in those born at term. During the course of the infectious and nutritional diseases it is always a dangerous sign when the blood pressure shows a marked and sustained decrease.

Hypertension is very seldom found in children without the clinical manifestations, but nevertheless records should be determined.

H. McC.

Lindenbaum, I., and Kapitzka, L.: The Clinical Picture and Pathological Histology of Buerger's Form of Thrombo-Angiitis Obliterans. Arch. f. klin. Chir. 184: 413, 1936.

The authors report a series of 22 cases. They emphasize particularly the phlebitis which accompanies the arterial manifestations of the disease and divide the cases into three stages consisting of (a) migrating phlebitis with little or no arterial symptoms, (b) migrating phlebitis with definite arterial symptoms, and (c) migrating phlebitis accompanied by arterial thrombosis. They advise sympathectomy for patients in the second stage and for those in the first with beginning arterial manifestations. Segments of inflamed superficial veins were removed for biopsy in sixteen patients. The clinical and histological pictures support the allergic theory as to the origin of the disease.

I. M. Z.

Fonia, A., and Vanotti, A.: New Experiments on the Origin of Thrombosis. Schweiz. med. Wchnschr. 64: 1086, 1934.

Experimental venous thrombosis produced in frogs' tongues was observed with the help of a capillary microscope. On coagulating the endothelial wall of a vessel with a platinum micro-electrothermocautery, spindle-shaped cells, which are the equivalent of human thrombocytes, accumulated at the place of the injury and covered it. This concentration of such cells continues over the injured wall until it entirely obliterates the vessel. The lowered rate of blood flow accelerates this procedure. Lowered rate of blood flow without injury of the epithelium does not produce thrombosis.

J. K.

Kraus, Herbert: Effect of Intravenous Injection of Different Iodine Preparations on the Peripheral Vessels. Nannyn-Schmiedbergs Arch. 179: 537, 1935.

Intra-arterial injection of drugs containing iodine, such as abrodil, uroselectan, and tenebryl, increased the peripheral circulation, due to dilation of the peripheral vessels. In experiments on rabbits and dogs, the peripheral vessels showed dilation after intravenous injection of such drugs, while in cold-blooded specimens the re-

action was absent. When pituitrin or adrenalin was administered previously, larger doses of these iodine preparations failed to produce vasodilation. The time of vasodilation was short, lasting only as long as the preparation remained adequately concentrated in the blood stream.

J. K.

Huggins, C. B., Blockson, B. H., and Wilson, Harwell: Thermal Changes in Local Asphyxia and Reactive Hyperemias. *Arch. Surg.* 32: 528, 1936.

Complete mechanical obstruction to the flow of arterial blood in man resulted in a gradual fall in temperature of the skin below the area of constriction and a slow but steady rise of the temperature in the control limb and above the tourniquet in the experimental limb. At the time of release there was a large increase in temperature above the initial readings in the limb to which the constriction had been applied and a sharp fall in the temperature of the skin of the control limb. A similar type of experiment on rabbits showed that the temperatures in the bone marrow and the muscles of the limb react similarly to that of the skin of man as a result of mechanical constriction. Partial asphyxia of the limb produced by distention of the constricting cuff to the diastolic blood pressure caused gradual diminution in the temperature of the skin of the extremity, which diminution continued after the tourniquet was removed. The injection of adrenalin into the femoral artery of dogs immediately after the removal of the tourniquet, which had produced complete asphyxia, prevented the hyperthermia which ordinarily follows the removal of the tourniquet. The injection of adrenalin directly into the femoral artery of dogs caused a gradual diminution of the temperature of the skin, which returned to normal in about two hours. Injection of adrenalin into the femoral artery of men caused a rise in the systemic blood pressure, tachycardia, and dyspnea. The experimental leg became cadaveric in appearance, and there was complete obliteration of the pulses in the dorsalis pedis and posterior tibial arteries. The temperature of the skin lessened. Recovery began in about twenty-five minutes after injection. Subcutaneous injection of adrenalin in the region of a subcutaneous thermocouple produced a marked fall in the temperature.

E. A.

Marcovich, P.: Peripheral Thermooscillometry. *Cuore* 19: No. 5, 1935.

The leg with oscillometer attached was immersed for five minutes in cold water at 7° C. and later for five minutes in warm water at 42° C. In normal conditions heat produced an increase, and cold caused a decrease in the oscillometric readings. Amyl nitrite had the same effect as heat on the oscillometric readings, but the reaction following administration of acetylcholine was so small that no definite conclusions could be made.

J. K.

Hustin, A.: Vasmotor Reactions in Men in Normal and Pathological Conditions. *Lyon Chir.* 32: 384, 1935.

On compressing one arm, the skin temperature of that member was lowered, but it quickly returned to normal upon relieving the compression. At the same time a brief temperature drop was observed in the other arm. It seems that compression prevents a contralateral vasoconstricting reflex which would be activated by the cooling of the compressed arm. Mental excitement lowered the skin temperature, while the rectal temperature remained unchanged. Immersion of one arm in cold water caused the skin temperature of the other arm to drop, because of a contralateral reflex. The temperature drop could be prevented by compressing the cooled arm.

Temperature studies during narcosis showed the following vasomotor changes: (1) vasoconstriction at the beginning stage, due to excitement; (2) vasodilation due to paralysis of the nerve center (in spinal anesthesia through interruption of the afferent reflexes); (3) constriction on return to consciousness; and (4) dilation. For three to four days following narcosis, the usual fluctuations in the skin temperature were absent.

Lumbar sympathectomy increases the skin temperature of the lower extremities, and their temperature approaches the rectal temperature. Sympathectomy seems to reduce the sensitiveness of the arteries to internal and external impulses. The same results are seen after periarterial sympathectomy—constant dilation of the vessels.

J. K.

Watson, Charles M., and James R: Autotransfusion in the Treatment of Wounds of the Heart, *J. A. M. A.* 106: 520, 1936.

Autotransfusion was used to combat the excessive loss of blood resulting from a stab wound of the heart. The blood was obtained from the pleural cavity during the operation, was filtered through gauze, and was injected intravenously.

As far as can be determined by a review of the literature, this is the first time autotransfusion has been used in the treatment of this type of injury. In view of its marked success in this instance, the authors believe that it should receive further trial as an adjunct to cardiorrhaphy in those cases in which the loss of blood is sufficient to threaten the immediate survival of the patient.

H. McC.

Sanders, C. E.: Cardiovascular and Peripheral Vascular Diseases: Treatment by a Motorized Oscillating Bed. *J. A. M. A.* 106: 916, 1936.

The bed described is equipped with motor and tilting device which alternately elevates and lowers the head and the foot. The starting and stopping and speed of the tilting are under control of the patient or attendant.

Its advantage is claimed to lie in the changing distribution of body weight it accomplishes, and in the use of gravity in altering the mechanical factors influencing impaired circulation, whether of cardiac or peripheral vascular origin.

L. H. H.

di Cio, Alfredo V.: Carbondioxide and Carbogen in the Therapy of Peripheral Arterial Diseases. *Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch.* 8: 201, 1935.

Filtrated gas was injected intradermally in the thigh. The beginning dosage, 250 c.c., was increased daily, according to the tolerance of the patient, to a maximum of 600 to 700 c.c. Absorption took place in from twelve to sixty hours. The best results were obtained with a mixture consisting of 95 per cent oxygen and 5 per cent carbon dioxide. There seemed to be objective and subjective improvement in cases of acrocyanosis and endarteritis obliterans.

J. K.

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Original Communications

THE INADEQUACY OF THE NORMAL COLLATERAL CORONARY CIRCULATION AND THE DYNAMIC FACTORS CONCERNED IN ITS DEVELOPMENT DURING SLOW CORONARY OCCLUSION*

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IN THE preceding paper¹ evidence was presented that, in normal hearts, drugs reputed to dilate coronary vessels cause no significant improvement in the collateral blood flow to an area rendered ischemic by occlusion of its main branch. The most natural interpretation of such results would be that if such communications exist they either are too small or have little power of vasomotor response. This revives the question as to the existence of a collateral coronary supply which has interested anatomists, pathologists, physiologists, and clinicians alike for many years. A critical revaluation of available evidence is therefore opportune.

The fact that infarction is the common sequel to coronary occlusion has long seemed sufficient to convince pathologists of the terminal character of the coronary vessels. Several reports²⁻⁷ of special instances in which complete occlusion of two coronary vessels was found post mortem without evidence of serious myocardial damage require the assumption that, at least under special conditions, adequate collateral anastomoses can develop. A review of our knowledge regarding the dynamic factors concerned in the development of a more generous collateral circulation is a second purpose of this communication.

THE CORONARY COLLATERAL SUPPLY IN NORMAL HEARTS

Within recent years, anatomical and clinicopathological studies utilizing injection methods have provided evidence that even in normal hearts communications exist between subdivisions of any large coronary ramus and (a) other coronary branches, (b) extracardiac branches, and (c) vascular and sinus channels communicating with the interiors of the right and left ventricles (Spaltcholtz,⁸ Campbell,⁹ Wearn,¹⁰

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Kretz,¹¹ Hudson, Moritz, and Wearn.¹² The inference should not be drawn, however, that such methods necessarily demonstrate the existence of a *functional circulation* during life or that such channels are of immediate value in the emergency of a sudden coronary occlusion. Such inferences ignore the most elementary dynamics of the coronary circulation. As clearly stated by W. T. Porter¹³ in 1900, "the passage of a fine injection-mass from one vascular area to another proves nothing concerning the possibility of one area receiving its blood supply from the other. Such a supply is impossible if the resistance in the communicating vessels is greater than the blood pressure in the smallest branches of the artery through which the supply must come. It is the fact of this high resistance due to the small size of the communicating branches which makes the artery *terminal*."

Experimental evidence for a time seemed to indicate that serviceable communications exist. Pratt¹⁴ caused a cat's heart to beat by feeding warm oxygenated blood into the right ventricular cavity. Blood which flowed from an incised vein on the surface had a dark hue indicating oxygen utilization. More recently Wiggers¹⁵ showed that drugs limited to the right ventricular cavity of a normal cat's heart which was perfused through the aorta produces typical stimulating and depressing reactions of the left ventricle. The inference was drawn that such drugs were distributed by sinusoidal vessels against higher pressures in the coronary arteries, although a lymphatic distribution could not be excluded. Batson and Bellet¹⁶ have presented evidence that, when injection of particulate matter incapable of passing the pulmonary capillaries causes fall of arterial and rise of right auricular pressure, particles are driven back into myocardial capillaries by venous channels.

Since the oxygen partial pressure of blood in the right heart is low and the blood is under relatively low hydrostatic pressure, it remains questionable, despite such demonstrations, whether these channels could be of much importance in providing sufficient oxygen for maintenance of contraction. Sizeable communications with the left ventricle (Wearn¹⁰) in which pressures are higher and the blood fully oxygenated would more probably be of service. Stella (1932), however, was unable to record any flow from the peripheral ends of coronary vessels, when all were temporarily ligated centrally, which discovery indicated that such a flow is practically nonexistent in normal hearts. At seeming variance with these conclusions were the observations of Bohning, Jochim, and Katz¹⁷ that particulate matter injected into the ventricular cavities under conditions in which access through coronary branches was precluded, nevertheless, found its way into ventricular capillaries, as demonstrated by subsequent histological examination.

We may summarize briefly recent evidence from our own laboratory which indicates that the flow through collaterals is normally in-

significant. In the previous paper¹ we alluded to the facts that the flow from the cut end of a peripheral coronary branch is exceedingly small and that its red color suggests that the small amount of blood that does escape has not passed through the muscle tissue. Gregg, Green, and Wiggers¹⁸ reported that the time relations of optical pressure pulses from a peripheral coronary vessel preclude the pressure rise during each systole from being due largely to transmission of pressure through collaterals, and that the peripheral coronary pressure does not rise with aortic pressure because of the transmission of greater pressure but rather because of increased action of the left ventricle. Tennant and Wiggers¹⁹ have shown that after ligation of a main coronary vessel the blood supply is so far reduced that contraction fails within one minute and Wiggers and Green¹ found that this cannot be prevented by drugs that elevate aortic pressure or act upon collateral vessels. To this H. Green (unpublished) added still other evidence. In hearts that fibrillated the three rami were dissected out and perfused with Locke's solution under different pressures. By using the technic described in the previous paper, the rate of inflow from 180-30 mm. declining pressures was then determined in the ramus descendens anterior while pressure in the other branches was changed from 30 up to 165 mm. No alteration of flow could be detected. If collateral intercoronary communications of significant size exist, significant differences in flow should have occurred when collateral pressure was changed. In still other experiments all coronary branches except the ramus anterior descendens were perfused at a constant pressure of 80 mm., and the intramural pressure was raised from an inconsequential level of 5-10 mm. to 150 mm. Hg. The run-off from the anterior ramus descendens under a declining pressure was similarly determined at these different intraventricular pressures. Again no alteration could be detected. Such evidence points to the negligible value of collateral communications with the ventricle when counterbalancing pressures exist in the main coronary vessels.

When critically reviewed, most of the experimental evidence favors the view that from a practical aspect the coronary branches are essentially terminal; anastomoses such as exist in normal hearts apparently have no functional value.

THE DEVELOPMENT OF COLLATERAL CIRCULATIONS UNDER PATHOLOGICAL CONDITIONS

It must be emphasized, however, that these different proofs of a negligible collateral supply in normal hearts do not preclude an increase in the caliber of potential communications or the development of new systems of vessels which can furnish adequate nourishment for the myocardium under pathological circumstances.

Four sources of compensatory collateral supply are possible when a main vessel is gradually occluded, viz., (1) through development of more extensive intercoronary communications, (2) through development of extracardiac anastomoses, (3) through enlargement of arterio-ventricular channels, and (4) through reversal of flow from cardiac veins to blood capillaries. Gross and Kugel²⁰ have described the more extensive anastomoses and larger territorial distribution of the left coronary system with advancing age, which may represent a biological compensation for increasing sclerotic changes. Hudson, Moritz, and Wearn¹² have described the extensive extracardiac communications that may develop in the human heart. Beck, Tiehy, and Moritz²¹ have shown experimentally that such invasion from extracardial branches can be induced surgically in dogs, so that following establishment of such a supply, the main branches can be ligated without fibrillation and the muscle continues to contract when studied myographically (Bright and Tennant²²). Robertson²³ found that when coronary vessels are slowly occluded by experimental procedures, collateral circulations occur preferentially from pericardial branches.

Factors Determining the Development of Collateral Channels.—It is commonly asserted that collateral circuits develop in regions of reduced blood supply because a need for more blood exists. *This is indeed a truism but not an explanation.* Some physical or biological mechanisms must be concerned in eventuation of the increased blood flow. The author now ventures to suggest that the slow establishment of differential pressure gradients during development of partial or complete occlusion of a main branch may distend normally useless vessels to a degree that they soon become pervious to blood. Such an initial encouragement of blood flow, though not large, would supply a source from which new vessels *that carry blood* could develop.

Since we now know the form and magnitude of the pressure changes that occur during each cycle in the left ventricle in the aorta and its branches, as well as in the peripheral end of a partially or totally occluded coronary artery, it is possible to establish the trends of flow that could occur provided adequate channels are present and to delineate the conditions under which a flow is impossible regardless of the existence of wide channels.

In Fig. 1 A, curve 1 represents pressure changes in the aorta and its immediate branches including the coronary vessels and curve 3, intraventricular pressure. The distance denoted by x represents isometric contraction, y , denotes systolic ejection and z denotes diastole. It is apparent that the pressure difference between the ventricular cavity and coronary branches is very slight during systolic ejection (y) and as indicated by arrows greatly in favor of a flow from the coronary arteries to the ventricular cavity during diastole (z). This directional gradient also exists during isometric contraction (x), although it becomes rapidly smaller as contraction proceeds. It is equally

obvious that at no time of the cycle does any pressure gradient exist between extracoronary or intercoronary branches; curve 1 essentially represents the pressure relations for all. Consequently it is dynamically inconceivable that any transfer of blood could occur via extracoronary anastomoses even if they were extremely large.

Let us now suppose that, as a result of gradual narrowing of a coronary branch, the pressure within this branch decreases. The pressure curve is then not only lower but changes its contour (curve 2 in Fig. 1 *B* and *C*). As indicated by arrows, the pressure gradients then become such that blood could move *from* the ventricular cavity to the coronary vessels during systole and in a reverse direction during diastole. As shown in Fig. 1 *C* the pressure gradients between intercoronary and extracoronary channels are favorable for a continuous

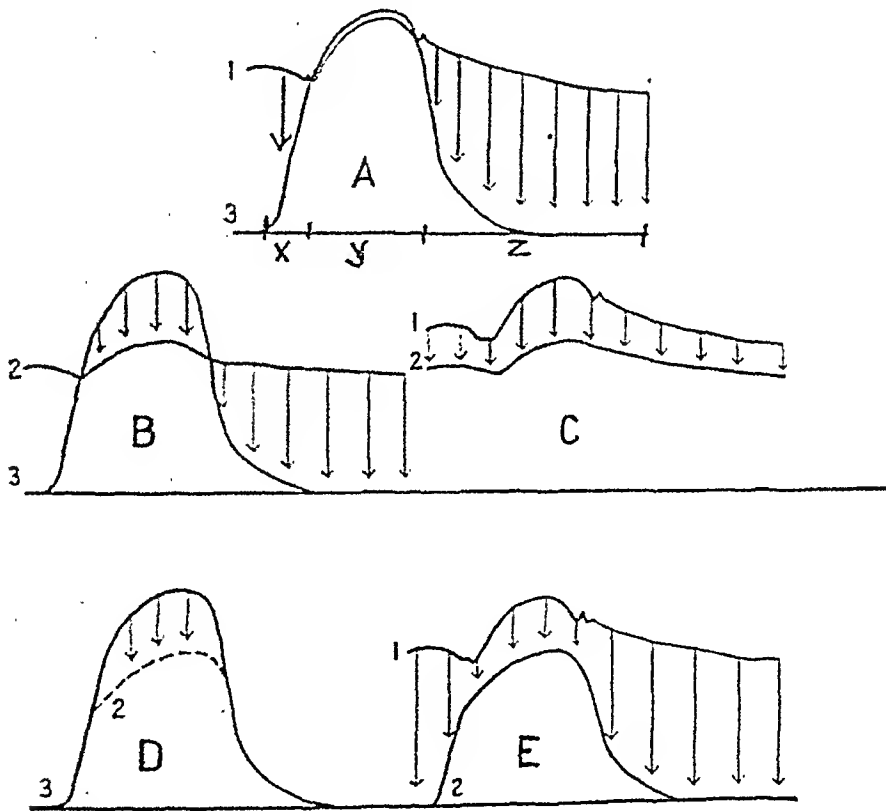


Fig. 1.—Series of curves showing differential pressures. *A*, between coronary vessels and left ventricle under normal conditions. *B*, same during partial occlusion. *C*, between partially occluded coronary and other arteries. *D*, between left ventricle and totally occluded coronary tributaries. *E*, between other arteries and coronary tributaries in occluded area. Discussion in text.

flow toward the ischemic area during systole as well as diastole. Upon general principles it might therefore be predicted that such communications would tend to develop more extensively than arterioventricular vessels, which prediction is in harmony with the experimental observation of Beck, Tiehy, and Moritz²¹ and of Robertson.²³ It also offers a reasonable explanation for the more extensive extracoronary communications discovered post mortem in human hearts in which some narrowing of the main arteries apparently exists.

The dynamic relations developed during complete occlusion of a coronary branch are represented by curves *D* and *E*. Curve 2 repre-

sents the contour and magnitude of pressure developed in peripheral coronary vessels, as established by optical records (Gregg, Green, and Wiggers¹⁸), and the upper curve 3 again represents intraventricular pressure. It is apparent that pressure gradients are again favorable for transfer of blood from the ventricular cavity to coronary arteries during systolic ejection but the great difference normally existing during diastole (curve A) is abrogated. It is therefore evident that physiological stimuli for development of such channels cannot be very potent. On the contrary, the great increase in pressure gradients between intercoronary and extracoronary branches shown in Fig. 1 E suggests that these vessels ought to have the better chance to develop.

Bellet, Gonley, and McMillan²⁴ from a microscopic study of a heart in which "the larger coronary arteries were completely occluded a short distance from their origin by tuberculous intimal involvement and by compression from a surrounding caseous tumor" concluded that the myocardium was nourished by dilatation of potential Thebesian channels. They postulate that closure of veins preceded occlusion of arteries and that arterial blood was forced to widen new channels of exit to the right auricle and ventricle. Upon subsequent closure of arteries these enlarged channels presumably nourished the myocardium from the right chambers. While their interpretation might apply to maintenance of blood supply to the right ventricle, a number of facts make such a supply to areas of the left ventricle less probable, viz., (1) right intraventricular tension does not exceed intramural tension in the left ventricle, (2) "relatively few (vascular spaces or sinusoidal channels) were present in the muscle of the left ventricle," and (3) the idea that occlusion of veins precedes closure of arteries was an inference, not a demonstrated fact. At any event such a mechanism could not operate after thrombotic occlusion which leaves the venous channels unobstructed.

SUMMARY

The evidence for and against the existence of a liberal collateral blood supply to the normal ventricular myocardium is reviewed. Evidence based on histological or injection studies is not conclusive as to the magnitude of such circulations. The volume flow through collateral vessels depends not only upon the size of communications but upon the magnitude of pressure differences. The presence of one without the other cannot result in flow. The experimental evidence is reviewed, and the conclusion is reached that in the normal heart collateral flow is extremely small and insufficient to support contractions in an area rendered ischemic by ligation of a main branch.

The existence of a negligible collateral supply in normal hearts does not preclude the enlargement of minute potential communications nor the development of new ones when a main branch is slowly occluded. In such cases, physiological mechanisms must exist to account for the

development of such circulations. The suggestion is made that, as a main branch is slowly occluded, the development of altered pressure gradients first distends normally useless channels and so furnishes a supply of blood under pressure for the newly growing vessels. The details of the probable pressure gradients are analyzed on the basis of known forces and magnitudes of the pressure variations throughout the cardiac cycle.

The essential conclusions reached are:

1. Dynamic pressure gradients are such that *normally* a transfer of blood *from* the coronary arteries *to* the ventricular cavities could occur during diastole and during the early part of isometric contractions (i.e., for perhaps 0.02 sec.) but no transfer could occur between intercoronary and coronary-extracoronary branches at any time.

2. When the size of a coronary branch is *reduced*, the pressure gradients are favorable for developing flow through intercoronary or extracoronary anastomoses throughout the cycle; and a flow *from* the ventricular cavity *to* the artery could occur during systolic ejection. During diastole the gradient of pressure favors a flow *toward* the ventricular cavity although the pressure differential is decreased in proportion to the narrowing. In other words a to-and-fro movement could occur during each heart cycle.

3. When a main coronary branch is *completely occluded*, the same pressure relations exist, except that no pressure gradient exists between coronary branches and the ventricular cavity during diastole.

4. It is improbable from dynamic considerations that reversed flow from the right heart through Thebesian veins plays any rôle in collateral supply to the left ventricle.

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THE SIGNIFICANCE OF RHEUMATIC FEVER IN THE ETIOLOGY OF CORONARY ARTERY DISEASE AND THROMBOSIS*

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IN A consideration of the causes of coronary artery disease and thrombosis it was evident that there had been some question as to the bearing of rheumatic fever on arteriosclerosis of the coronary arteries. The clinical and pathological aspects of both rheumatic and arteriosclerotic heart disease are well known. The occurrence of each is a commonplace in clinical practice. The pathological association, however, of rheumatic fever with arteriosclerotic heart disease is apparently uncommon. Reference to the older authors reveals no mention of their occurrence together, and Levine,¹ in his study of coronary thrombosis, stated that in the presence of the one lesion the other could practically be eliminated from consideration. There have been cases reported, however, in which both these types of heart disease were found simultaneously. We were interested in determining the reason, if any, other than pathological coincidence for this fact. We then analyzed the post-mortem material at Montefiore Hospital, comprising 3,264 cases during the past seventeen years, and found thirty instances, or 0.91 per cent, in which both types, coronary arteriosclerosis and rheumatic valvular disease, occurred together.

REVIEW OF LITERATURE ON RHEUMATIC CORONARY DISEASE

It is now generally accepted that active rheumatic fever causes changes in the coronary vessels of the heart as in other branches of the circulatory system. Cowan,² in a study of twenty-five cases of rheumatic disease, found in every instance some increase of connective tissue; and in two instances, in both of which the coronary arteries were damaged, muscular fibrosis was considerable. Though myocardial fibrosis may be due to rheumatic fever, in view of the associated coronary sclerosis, the myocardial damage was probably secondary to vascular disease. Kahn³ is of the opinion that rheumatic fever has been inadequately stressed as a cause of coronary sclerosis, and in twenty-four out of eighty-two cases of angina pectoris he obtained a history of rheumatic fever or other acute infection. Krehl⁴ described intimal changes and thickening of the walls of the smaller vessels in acute rheumatic fever, with stenosis of the lumina, hyaline changes, and round cell infiltrations of the vessel

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walls. Romberg⁵ cited a case of Leyden,⁶ one of thrombosis of the coronary vessels in the course of acute rheumatic fever. The former observed hyaline thrombi in medium-sized and small vessels, as well as numerous venous thromboses, periarteritis, and adventitial infiltrations. Aschoff⁷ reported similar observations. Geipel⁸ and, likewise, Watjen,⁹ recorded endarteritic proliferation in medium- and small-sized vessels with exquisite disturbances in the internal elastic lamella. Both Kaufmann¹⁰ and Jores¹¹ observed rheumatic endarteritis of the major vessels, the former also noting the lesion in the coronaries. The latter referred to Heydloff,¹² who had a case of verrucous arteritis of the carotid and innominate arteries. Raiche¹³ reported a case of verrucous arteritis of the pulmonary artery. MacCallum¹⁴ believed that coronary arteritis, arteriolar thromboses, and necroses occurred only in the severer attacks of rheumatic fever. He conjectured that extreme myocardial disability might be due to occlusion of the vessels or to their compression by adjacent Aschoff bodies. He observed focal lesions in the walls of the aorta. Rheumatic involvement of the coronary artery, aorta, celiac axis, superior mesentery, and renal arteries was described by Pappenheimer and von Glahn¹⁵ in a male child of fifteen years. In nine fatal cases of rheumatic fever, all in patients under twenty years of age, Perry¹⁶ described changes involving all the coats of the vessels. One of the patients, a male child fourteen years old, had anginal seizures and at necropsy a thrombus was found in the left coronary artery. Coronary artery involvement during acute rheumatic fever has been diagnosed clinically by Slater.^{17, 18} The diagnosis is, however, open to question since, as pointed out by Swift and Cohn¹⁹ and by Rothschild, Sacks, and Libman,²⁰ abnormal electrocardiograms frequently occur in acute rheumatic fever. Abnormal electrocardiograms have also been observed in acute pericarditis by Porte and Pardee.²¹ Rothschild, Kugel, and Gross,²² as well as White,²³ have observed coronary arteriosclerosis complicating rheumatic heart disease. Karsner and Bayless²⁴ recently expressed the view that rheumatism predisposes to coronary artery sclerosis, though they admit that they have not conclusively shown that coronary sclerosis is dependent upon the acute degenerative and inflammatory lesions associated with acute rheumatic fever.

ANALYSIS OF MATERIAL

Two problems have presented themselves:

1. Whether in these thirty cases the association of the coronary artery disease and the rheumatic valvular lesion was not purely coincidental.
2. Whether the coronary sclerosis represented a degenerative lesion superimposed on coronary arteries previously damaged by rheumatic fever and, therefore, predisposed to coronary sclerosis.

Age Groupings.—The ages of the patients showed a wide diversity ranging from twenty-nine to ninety-one years, with an average age of fifty-six. This figure compares closely with that of Levine¹ for nonrheumatic coronary cases, the average age of his patients being 57.8 years.

Divided into age groups the cases may be classified as follows:

	FEMALES	MALES
20-30	2	0
31-40	0	0
41-50	3	3
51-60	2	6
61-70	5	6
71-80	2	0
81 and over	1	0
	<hr/> 15	<hr/> 15

The cases are equally divided between the two sexes, though this series is too small to base any specific conclusions as to the significance of sex. It appears, nevertheless, that the combination of the two lesions appeared earlier in females. It is also noteworthy that individual longevity is greater in the female group. The usual preponderance of males in coronary disease is not evident in this series. The reason for this may be that rheumatic valvular lesions and essential hypertension are both more common in females, the latter disease predisposing them to coronary artery sclerosis.

Pathological Findings

Valvular Lesions.—There was mitral disease in 29 out of 30 cases, and in 23 mitral stenosis and insufficiency. In 6 cases there was mitral endocarditis, but in 4 of the latter no deformity of the valves. Nine had valvular disease of the mitral valve only. In 19 the mitral and aortic valves were affected. In 1, the involvement was limited to the aortic valve; in 2 others, to the mitral, aortic, and tricuspid valves. In another, in addition to the pulmonic, the mitral and aortic valves were involved. In 1 case there was also infective endocarditis of the mitral and aortic valves.

Arteriosclerotic Lesions of the Arteries.—Reference to Table I reveals the vascular lesions as well as the correlation between the vessels involved and the site of the myocardial infarction. It is noteworthy that in seventeen cases the right coronary artery was involved, and in three of these the involvement of the right was greater than that of the left. In the remaining fourteen both right and left were affected. Recently observations have come to light indicating that the right coronary artery is more commonly involved than is generally accepted. The frequency of involvement of the right coronary artery in this material is striking and raises the question as to whether the physiological work hyper-

trophy of the right ventricle secondary to mitral stenosis is a factor in sclerosis of this vessel. This question can be answered only from further study of the problem.

Cardiac Hypertrophy.—Cardiac hypertrophy was present in every case, the heart weights ranging from 380 to 900 gm. In fourteen there was known hypertension in addition to valvular lesions. In a number of cases with normal blood pressure it is possible that the coronary artery disease lowered an antecedent hypertension. Of six cases with normal blood pressure, one had severe coronary disease and aortic insufficiency, and the heart weighed 900 gm., while the other five weighed between 380 and 420 gm. In three of these there was gross evidence of cardiac hypertrophy, and in these and in the remaining two, there was microscopic hypertrophy. The weights of several hearts were not reported, but these also showed generalized cardiac hypertrophy. In all our cases, then, cardiac hypertrophy, either grossly or microscopically, was present. Whether this was caused by the valvular lesion or the hypertension, it is impossible to say.

It has been possible to correlate the heart weight and the blood pressure figures in some of these cases. Of those with hypertension the hearts in ten weighed 400 gm. or more; in one instance with aortic insufficiency and systolic and diastolic hypertension, the heart weighed 900 gm. A relatively small heart is compatible with hypertension since the heart may not increase in size although hypertension exists for many years.

Rheumatic Activity.—There were signs of rheumatic activity in sixteen of the thirty cases, constituting about 53 per cent of the material. The ages of these patients ranged from twenty-nine to seventy years. All, with the exception of 2, were forty-five years or over. The occurrence of frank carditis at these ages is unusual. Of 3 patients with old mitral lesions, one showed endocarditis of the aortic valve and the others, endocarditis of the mitral and aortic valves. Of 5 patients with mitral stenosis and insufficiency, 2 had acute endocarditis of the mitral and aortic and 3 of the mitral valve alone. Six had old double lesions of the mitral valve and aortic insufficiency. Of these, one had acute endocarditis of the aortic valve, 3 had endocarditis of the mitral valve, one, acute endocarditis of the mitral and aortic valves and another, endocarditis of the left auricle. There were 3 instances of tricuspid disease, including one of tricuspid stenosis associated with mitral stenosis and insufficiency and aortic insufficiency. Of these, one had healed endocarditis of the mitral valve, another healed endocarditis of the mitral and aortic valves, and the patient with tricuspid stenosis showed acute endocarditis of the aortic valve and healed endocarditis of the left auricle. Every patient with active rheumatic fever had frank congestive failure. Though carditis is the most significant cause of congestive

TABLE I

NO. SEX AGE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT CORONARY ARTERY	LEFT CORONARY ARTERY	VALVE LESIONS	RHEUMATIC ACTIVITY	ELECTROCARDIOGRAMS
1 F 45	Myomalacia				Mitral stenosis and insufficiency	Acute verrucous endocarditis of mitral and aortic valves; thrombi in right auricular appendage	
2 F 43		Fibrosis of ventricle; apical infarction		Left anterior descending occluded	Mitral stenosis and insufficiency; aortic insufficiency	Acute endocarditis of mitral valve	
3 F 29		Fibers coarser than average; increased connective tissue	Slight scattered atheromatosis		Mitral insufficiency; mitral stenosis?		
4 F 56		Posterior wall and interventricular septum extensively scarred	Marked calcification; lumina almost occluded	Marked narrowing	Mitral stenosis and insufficiency; aortic insufficiency; tricuspid valves shortened and thickened	Healed rheumatic endocarditis of mitral valve	
5 M 46	Pericarditis	Auto-mortem thrombus	Slight arteriosclerosis		Mitral stenosis and insufficiency; aortic insufficiency; tricuspid stenosis	Acute endocarditis of aortic valve; collections of cells suggestive of Aschoff bodies; healed lesion L.A., pericarditis R.V.	L.V.P. P-wave split in Leads I and II

TABLE I—CONT'D

NO.	SEX	AGE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT CORONARY ARTERY	LEFT CORONARY ARTERY	VALVE LESIONS	RHEUMATIC ACTIVITY	ELECTROCARDIOGRAMS
6	M	64		Ventricular aneurysm	Coronaries pipestem everywhere	Base of mitral valve calcified	Recent and healed endocarditis of aortic valve; fibrinopurulent pericarditis		
7	M	53		Infarct of posterior wall, fibrous streaking	Scattered atheromatosis		Mitral stenosis and insufficiency; aortic insufficiency		R.V.P., auricular fibrillation, negative T-waves all leads. Digitalis?
8	M	54	Extensive subendocardial fibrosis and hemorrhage	Slight apical thinning and fibrosis	Anterior descending, markedly narrowed, almost occluded		Mitral stenosis and insufficiency		Auricular fibrillation; unusually deep Q ₃
9	F	64		Grayish streaking	Adherent granular thrombus of transverse		Mitral stenosis and insufficiency; aortic insufficiency	Healing recent endocarditis of mitral valve	
10	F	62	Large irregular patch subendocardial fibrosis	Lumen markedly narrowed at sinus; more involved than left	Lumen markedly narrowed		Calcification at base of mitral and aortic valve leaflets; thickening and rolling of cusps, fusion of commissures, and calcification of pulmonic valve		L.V.P. Auricular fibrillation; P ₂ large; peak notching of QRS complexes; T ₂ and T ₃ inverted
11	F	29			Large branch almost completely occluded		Mitral insufficiency; mitral stenosis?	Healing endocarditis of mitral valve	Sinus rhythm

TABLE I—Cont'd

NO. SEX AGE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT CORONARY ARTERY	LEFT CORONARY ARTERY	VALVE LESIONS	RHEUMATIC ACTIVITY	ELECTROCARDIOGRAMS
12 F 70		Posterior wall and apex thinned; fibrosis of papillary muscles; adherent mural thrombus	Mouth markedly sclerosed; transverse and posterior descending markedly sclerosed	Anterior descending and transverse markedly sclerosed	Mitral stenosis and insufficiency, calcified vegetation on aortic above cusps	Healed recent endocarditis of mitral valve	L.V.P.
13 M 60		Mottled area in posterior wall	Red thrombus with occlusion; similar thrombus in a branch supplying posterior wall of left ventricle.	Minimal arteriosclerosis	Mitral stenosis and insufficiency; aortic insufficiency	Healed endocarditis of left auricle	Intraventricular conduction defect, prominent Q ₃
14 M 58			Extensive diffuse atheromatosis, no narrowing		Mitral stenosis and insufficiency; aortic insufficiency; sclerosis of aortic valves		L.V.P. Auricular fibrillation; myocardial damage
15 F 72			Arteriosclerosis and calcification of both, no narrowing		Mitral valve shows old lesions, valve not deformed; sclerosis of aortic valve	Healed rheumatic endocarditis of mitral valve	L.V.P.
16 F 60			Slight arteriosclerosis of ant. descending; other branches less involved		Mitral stenosis and insufficiency, leaflets fused		Auricular fibrillation, rapid ventricular rate; low voltage

TABLE I--CONT'D

NO.	SEX	AGE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT CORONARY ARTERY	LEFT CORONARY ARTERY	VALVE LESIONS	RHEUMATIC ACTIVITY	ELECTROCARDIOGRAMS
17	M	52		Infarct of posterior wall	Sclerosis of transv., double ostium of main stem with infarctive polyps overlying ostia	Narrowing of anterior descending ramus	Aortic insufficiency, subacute bacterial endocarditis of aortic valve with similar involvement of aortic leaflet of mitral valve		T ₂ and T ₃ inverted, high take-off of T ₁ subsequently all T-waves inverted and prominent Q ₃
18	M	40	Muscle fibers larger than left; parenchymal degeneration	Thinner than normal; marked pericardial degeneration	Mouths of vessels slightly reduced by arteriosclerosis		Mitral stenosis and insufficiency; aortic insufficiency; healed vegetations on tricuspid valve	Healed endocarditis of mitral and aortic valves	R.V.P., auricular fibrillation, low voltage
19	M	67		Fibrosis of posterior wall	Arteriosclerosis of sinus of Valsalva and artery	Marked arteriosclerosis of anterior descending and transverse rami	Mitral stenosis and insufficiency; aortic insufficiency		L.V.P. Subsequently auricular fibrillation and rapid ventricular rate
20	M	62		Fibrosis of wall and septum with bulging of latter	Slight thickening of coronary arteries		Mitral stenosis and insufficiency; aortic insufficiency	Thrombotic material--early endocarditis beneath line of closure of aortic valve; fine injected vessels at base of cusps	Low voltage, subsequently complete A-V dissociation; rapid ventricular rate

TABLE I—Cont'd

NO. SEX AGE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT CORONARY ARTERY	LEFT CORONARY ARTERY	VALVE LESIONS	RHEUMATIC ACTIVITY	ELECTROCARDIOGRAMS
21 F 46		Infarct of wall and midportion of septum with areas of hemorrhage and fibrosis; recent infarct	Marked sclerosis; no occlusion	Marked sclerosis; recent thrombus in anterior descending ramus	Mitral stenosis and insufficiency; aortic insufficiency		R.V.P. Auricular fibrillation with rapid ventricular rate; inversion of all T waves (digitalis?)
22 F 59	Pericarditis over apex	Infarct of anterior wall and apex	Arteriosclerosis; reduced	lumen slightly reduced	Mitral stenosis and insufficiency; aortic insufficiency	Healed and recent endocarditis of mitral valve	L.V.P. Auricular fibrillation. T _i and T ₂ inverted
23 F 61		Fibrosis of papillary muscle; infarct in midportion of lateral wall	No abnormalities	Anterior descending branch markedly sclerotic and occluded half inch from its mouth	Mesial leaflets of mitral valve thickened along edge; aortic valve rolled and thickened, chordae tendineae shortened		QRS notched and slurred, T _i and T ₂ inverted, subsequently bundle-branch and aortic block
24 M 57		Fibrosis of apex and lower fourth of septum	Arteries thickened and rigid tubes with calcification of lumen most marked in left	and felt as enlarged with marked reduction of lumen	Bicuspid aortic valve, several calcified nodules on aortic valve and slight thickening of posterior cusp		L.V.P. Premature auricular beats

TABLE I—CONT'D

NO.	SEX	AGE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT CORONARY ARTERY	LEFT CORONARY ARTERY	VALVE LESIONS	RHEUMATIC ACTIVITY	ELECTROCARDIOGRAMS
25	M	41		Opaque areas up to 1.5 cm. of apex, posterior wall, and septum		Narrowing of lumen of anterior descending ramus, circumflex occluded	Marked stenosis of mitral valve fusion of free edge which has calcified vegetation and fusion and thickening of chordae; fusion of aortic valves with obliteration of cusps		R.V.P. Premature ventricular beats
26	F	91		Muscle fibers coarser than average	Vessels diffusely pipestem; with marked stenosis of lumina but no complete occlusion		Mitral stenosis and insufficiency; calcification of mitral valve; aortic insufficiency with calcareous deposits under surface of valve; organized thrombus attached to posterior cusp		
27	M	60		Fibrosis of anterior wall near septum	Markedly calcareous	Anterior descending ramus almost occluded	Mitral insufficiency	Endocarditis of mitral and aortic valves	
28	M	55		Scarred areas up to 4 mm.	Mouths of both narrowed by atheromata; circumflex of both involved		Mitral stenosis and insufficiency	Healing endocarditis of mitral and aortic valves	L.V.P. Auricular fibrillation; low voltage
29	M	63		Grayish white fibrous tissue striations	Vessels extremely sclerosed and calcified throughout courses		Mitral stenosis and insufficiency	Old verrucae of mitral valve	
30	M	61			Coronary arteries thickened throughout, encroaching on lumina to various degrees, in some areas marked		Mitral stenosis and insufficiency; aortic insufficiency	Endocarditis of mitral and aortic valves	L.V.P. Sinus arrhythmia; premature and blocked auricular beat

failure in patients with rheumatic heart disease, the association of hypertension, coronary disease, or both, makes it impossible to determine which factor or factors produced the congestive failure.

The blood pressure figures varied a great deal, from 107 to 225 mm. of Hg systolic and from 64 to 104 diastolic. Fourteen patients had blood pressure figures of 150 or over, and nine patients, 160 systolic or higher. In 10, the diastolic pressure was 100 or over. Every patient with diastolic hypertension also had systolic hypertension. Hypertension may have been a compensatory phenomenon secondary to aortic insufficiency in some of the cases.

Angina Pectoris.—There was a history of angina pectoris in 14 cases; of these, 9 were in females and 5 in males. The preponderance of females, despite the usually greater frequency of arterial disease and angina pectoris in males, is an interesting disparity. Six had attacks of dyspnea. In 3 males the attacks occurred nocturnally; in 2 females both diurnally and nocturnally; and in one female, diurnally only. Five patients had both paroxysmal dyspnea and angina pectoris. Paroxysmal dyspnea is frequently indicative of coronary disease and is especially significant in hyposensitive individuals who give no anginal history.

In nine cases no anginal syndrome was present. Several reasons may account for this fact: (1) an inadequate history; (2) in a number of instances the clinical picture could be accounted for by one type of cardiac lesion so that no further etiological factor was sought; (3) in a number of cases another condition like pulmonary tuberculosis or malignancy overshadowed the symptoms which could have been attributed to cardiac disease; (4) in several, the vascular or valvular abnormality was so insignificant that it produced no symptoms and was purely of pathological interest; (5) other cases presented silent coronary thrombosis, and the diagnosis was made only by routine electrocardiographic examination or at the necropsy table.

Complications

Congestive Heart Failure.—Congestive failure was a striking feature in all the patients except two. One of the latter died an acute cardiac death. The factors concerned in the production of heart failure have already been referred to.

There was auricular fibrillation in 10 cases, and in all but one of these congestive heart failure was present. Eleven had sinus rhythm, and in all but one there was associated congestive failure. There were 4 cases of intraventricular conduction defect, and in all of these also there was congestive failure. It was difficult to correlate the circulatory failure with the auricular fibrillation as there were many other contributory factors.

As noted above, subacute bacterial endocarditis was present in one instance, superimposed on old rheumatic mitral and aortic valves with polyps of subacute bacterial endocarditis overhanging the double ostium of the right coronary artery.

The association of diabetes mellitus with arterial disease, and particularly coronary disease, is well known. In Levine's cases¹ the incidence was very high, about 24 per cent. Nathanson²⁵ in a recent study of 100 necropsies on diabetic patients found that 52.5 per cent had coronary disease, whereas only 8 per cent of nondiabetic subjects had coronary arteriosclerosis. So common is the occurrence of diabetes in arteriosclerotic heart disease that Levine believes it is second in importance only to hypertension. Whether the two diseases occur simply coincidentally in the same type of individual, as Enklewitz²⁶ maintains, or whether diabetes is a factor in the causation of coronary sclerosis, is still an open question, though the frequent association of the two is beyond dispute. Clinical diabetes was strikingly absent in our material. One patient had a trace of sugar in the urine on one occasion. Another had a blood sugar level of 165 mg. but no glycosuria. In the latter patient we may have been dealing with a high threshold for sugar due to arteriolar renal disease secondary to hypertension.

Electrocardiographic Findings

Electrocardiographic tracings were available in twenty-one cases. Five showed left axis deviation. Of these, Case 12 showed at necropsy extensive involvement of all the coronary arteries and an infarct of the posterior wall and apex. Cases 15 and 30 showed extensive coronary sclerosis and calcification but no infarction. Another patient (Case 5) with slight coronary sclerosis had an ante-mortem thrombus in the left ventricle. Case 24 showed extensive calcification of the coronary arteries and fibrosis of the apex and lower fourth of the septum. One patient (Case 11) with sinus rhythm had marked narrowing of a large branch of the left coronary artery but no myocardial lesion. A patient (Case 25) with right axis deviation and premature ventricular beats showed areas of fibrosis of the septum, apex, and posterior wall of the left ventricle, narrowing of the anterior descending ramus, and occlusion of the transverse branch of the left coronary artery.

Auricular fibrillation was reported in 10 cases, 5 with left, 3 with right, and 2 with no axis deviation. Of the five with left axis deviation, one case (Case 10), with inversion of the T-waves in Leads II and III and notching of the QRS complexes, showed a large patch of subendocardial fibrosis of the left ventricle and greater involvement of the right than the left coronary artery. In the second case (Case 14), in which the electrocardiogram showed also myocardial damage, the coronary arteries were diffusely atheromatous, but there was no myocardial fibrosis or infarction. The third patient (Case 19), who had also a

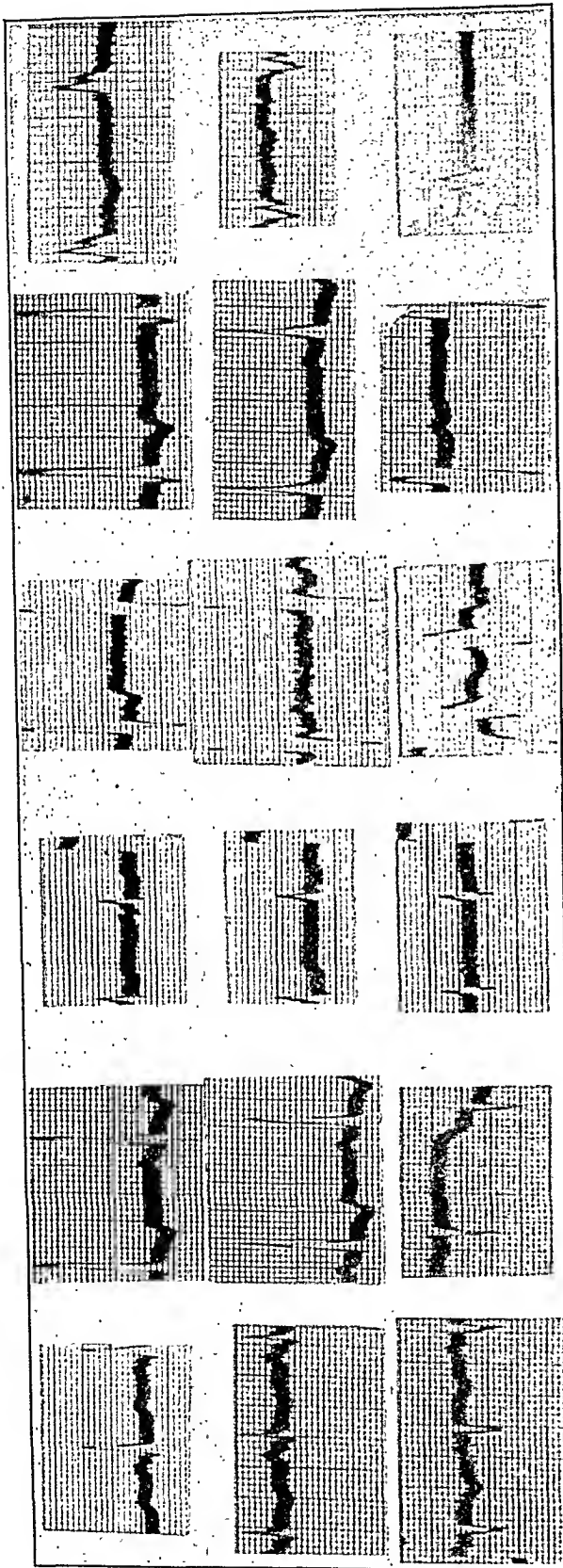


Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 1.—Case 10. Left axis deviation large P₂, notching of QRS, inversion of T₂ and T₃. Necropsy: Marked narrowing of right coronary at sinus of Valsalva, lumen of left markedly narrowed, large irregular patch of subendocardial fibrosis in left ventricle.

Fig. 2.—Case 13. Intraventricular conduction disturbance, T₁ and T₂ negative, prominent Q₂. Necropsy: Recent thrombosis of right coronary and a branch of right supplying posterior wall of left ventricle, minimal arteriosclerosis of left, mottled area in posterior wall of left ventricle.

Fig. 3.—Case 20. A-V dissociation. T₁ and T₂ partly negative. Necropsy: Slight thickening of coronary arteries, fibrosis of left ventricle and septum.

Fig. 4.—Case 11. Left axis deviations, auricular fibrillation, partly negative T₁ and T₂, intraventricular conduction disturbance; T₁ below isoelectric line, unusually high take-off of T₃. Necropsy: Rheumatic mitral and aortic disease, extensive diffuse coronary atherosclerosis, coronaries everywhere patent, no infarction.

Fig. 5.—Case 23. Left axis deviation, intraventricular disturbance, negative T₁ and T₂.

Fig. 6.—Comparison record, same case, twenty months later. Auricular fibrillation, atherization block. Necropsy: Marked sclerosis and occlusion of left anterior descending branch, fibrosis of papillary muscle and infarct of lateral wall of left ventricle.

rapid ventricular rate, at necropsy presented fibrosis of the posterior wall of the left ventricle, with marked arteriosclerosis of both right and left coronary arteries. The fourth case (Case 22) showed inversion of the T-waves in Leads I and II and had an infarct of the apex and anterior wall of the left ventricle, with diffuse coronary sclerosis conforming to the T_1 type of electrocardiogram. The fifth case (Case 28) showed also low voltage and, post mortem, diffuse scarring of the left ventricle and marked sclerosis of both coronary arteries. Of 2 patients with auricular fibrillation, with right axis deviation and inversion of the T-waves in all leads, one patient (Case 7) had an infarct of the posterior wall of the left ventricle and diffuse fibrous streaking. The second

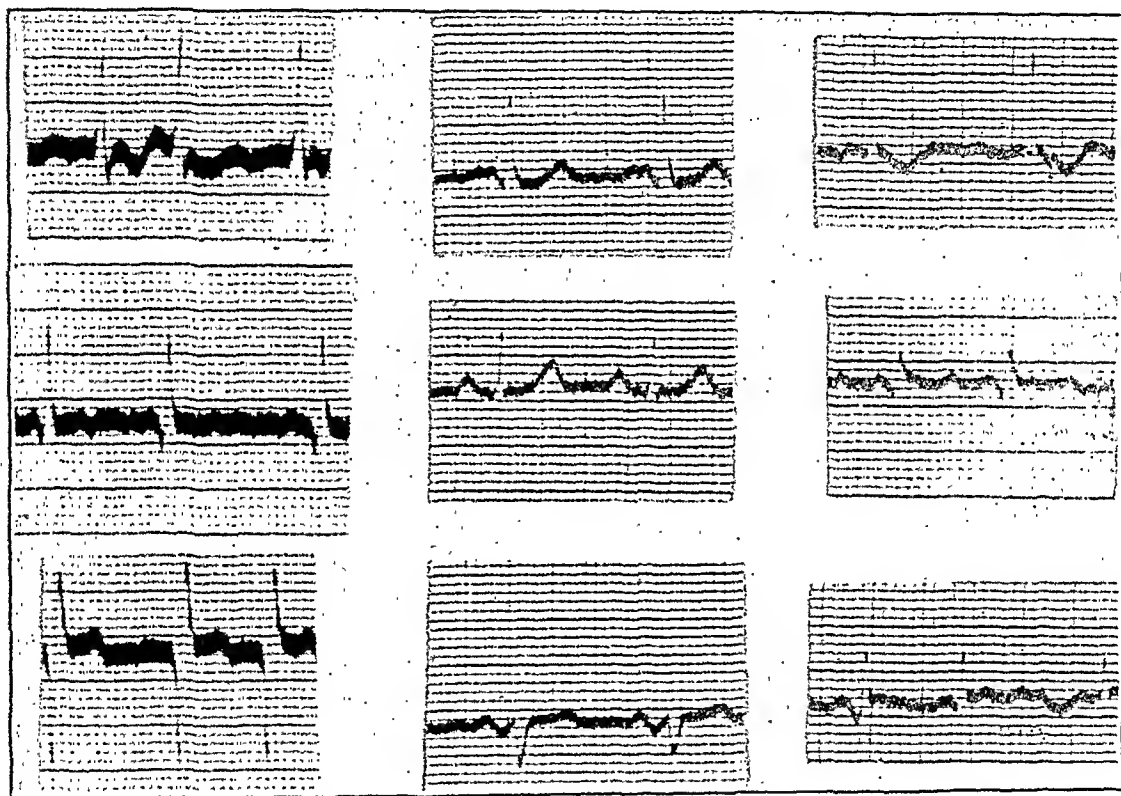


Fig. 7.

Fig. 8.

Fig. 9.

Fig. 7.—Case 8. Auricular fibrillation, negative T_1 and T_2 , abnormal R-T transition, prominent Q_2 . Necropsy: Marked narrowing of left anterior descending ramus, extensive subendocardial fibrosis and hemorrhage in right ventricle, apical thinning, and fibrosis of left ventricle.

Fig. 8.—Case still under observation. Left axis deviation with slurring of complexes.

Fig. 9.—Comparison record, same case, eight months later, following anginal seizure. Auricular fibrillation, negative T_1 and T_2 , abnormal R-T transition, prominent Q_2 and Q_3 .

(Case 21) with scattered coronary atheromatosis showed hemorrhage and recent infarction of the left ventricle and septum and marked arteriosclerosis of both coronary arteries. In a case of right axis deviation, auricular fibrillation and low voltage, necropsy revealed fibrosis of both ventricles and diffuse coronary arteriosclerosis. In an instance (Case 8) of auricular fibrillation with an unusually deep Q-wave in Lead III, at necropsy there were extensive subendocardial fibrosis and fresh hemorrhage in the right ventricle, apical thinning and fibrosis of

the left ventricle, and marked narrowing, with almost complete occlusion of the anterior descending branch of the left coronary. Another patient (Case 16) with auricular fibrillation, a rapid ventricular rate, and low voltage had slight arteriosclerosis of the anterior descending branch of the left coronary artery and no myocardial damage.

Marked intraventricular conduction defect occurred in 4 cases. Of these, 2 (Cases 13 and 17) with prominent Q-waves in Lead III showed posterior wall infarcts. Both had diffuse coronary arteriosclerosis with marked involvement of the right coronary artery, including recent multiple thromboses of that vessel in Case 13. Case 17 also showed abnormal R-T transition, with a high take-off of the T-wave in Lead III and inversion of all T-waves. This case presented, in addition, vegetations of subacute bacterial endocarditis overhanging the double ostium of the right coronary artery. In another case (Case 20) low voltage was followed by complete A-V dissociation and a rapid ventricular rate. The anatomical findings were fibrosis of the wall of the left ventricle and interventricular septum, with bulging of the latter and slight thickening of the coronary arteries. The electrocardiogram in Case 23 showed notching and slurring of the QRS complexes and inversion of the T-waves in Leads I and II. Subsequently, bundle-branch and arborization block developed. Post-mortem examination showed fibrosis of the apex and lower fourth of the septum, with diffuse calcification of the coronary arteries but slight reduction of the lumina, most marked on the left.

Prominent Q-waves were found in 4 cases. Three of these (Cases 8, 13, and 17) showed extensive vascular and muscular damage at necropsy. There were infarcts of the posterior wall of the left ventricle in 2 (Cases 13 and 17) and recent and old infarctions of the right ventricle and apical thinning and fibrosis of the left ventricle in the third (Case 8). The last patient, still under observation, following an anginal seizure, developed paroxysmal auricular fibrillation, a high take-off of the T-wave in Lead III, and prominent Q-waves in Leads II and III. Prominent Q-waves, especially in Lead III, have frequently been observed in coronary disease. Fenichel and Kugell²⁷ observed posterior wall lesions in all their patients presenting deep Q-waves in Lead III. Large Q-waves may, however, appear in advanced rheumatic heart disease, in congenital heart disease, and in disturbances of the mass relationships of heart muscle and septal displacement without coronary disease.

DISCUSSION

In our analysis we posed as our first problem the question as to whether the occurrence of arteriosclerotic and rheumatic heart disease was purely coincidental. Of the 3,264 necropsies in the records of Montefiore Hospital, the pathological association of coronary arterio-

sclerosis has been found in only thirty cases with rheumatic valvular disease. This association of the two diseases has thus been observed to be extremely rare. It is suspected that the association may have been purely coincidental. We found that either the valvular or the vascular lesion predominated and apparently was responsible for the clinical picture observed during life. There was no proved etiological relationship between the initial valvular lesion and the subsequent development of coronary arteriosclerosis.

Karsner and Bayless,²⁴ however, are of the belief that rheumatic fever, an inflammatory process, with an onset essentially early in life, predisposes to the premature development of coronary arteriosclerosis, a degenerative disease occurring predominantly in the middle and late periods of life. In any given case it is difficult to exclude antecedent rheumatic coronary arteritis as an etiological factor in coronary sclerosis or thrombosis. Study of our material, however, leads us to think that the two lesions may be independent and unrelated. If there were such a causal relationship, we should expect coronary arteriosclerosis with greater frequency at an earlier age in patients with rheumatic heart disease. The coronary arteries of young patients with rheumatic heart disease are usually free of arteriosclerotic changes. In short, although we cannot affirm or deny a relationship between rheumatic infection and coronary sclerosis, from the evidence before us we are inclined to believe the association is purely coincidental, and furthermore, we know that such patients live to about the same age as do the arteriosclerotic patients.

Despite the rather frequent involvement of the coronary arteries during the course of acute rheumatic fever, it has not been possible to establish such an entity on clinical grounds. To diagnose coronary disease from the electrocardiogram is unsafe. Published electrocardiograms indicating such relationship are equivocal, since similar findings may appear during acute rheumatic fever, aortic insufficiency, pericarditis, or coma. Recently attention has been called by Hochrein²⁵ to anginal episodes during quiescent rheumatic mitral stenosis resulting from narrowing of the coronary ostia by alterations in the mass relationships of the heart muscles. In aortic insufficiency particularly, severe anginal seizures are quite common. Schwartz²⁶ and, recently, Christian²⁷ have called attention to this phenomenon. Electrocardiograms in such cases may resemble those seen in coronary disease. These conditions have to be differentiated from rheumatic valvular disease with an accompanying coronary sclerosis. They are, however, usually sufficiently clear-cut entities to offer no difficulty in making a correct diagnosis.

Though the association of rheumatic valvular disease and coronary sclerosis is a rarity and the diagnosis is difficult, it has seemed to us that in some cases such a diagnosis might be suspected. In an individual with signs and symptoms of rheumatic heart disease who survives middle

life and later develops anginal pain, not attributable to aortic disease, active rheumatic fever, or pericarditis, the coexistence of coronary disease is to be suspected. Rare cases of angina pectoris in mitral stenosis without evidence of active rheumatic fever occur. In the absence of aortic insufficiency, an electrocardiogram may be of great help.

In two cases the diagnosis was made during life. One patient (Case 21) had hypertension, auricular fibrillation, and anginal seizures thought not to be due to rheumatic fever. The electrocardiogram showed evidence of myocardial damage, and at necropsy both coronary sclerosis and rheumatic valvular disease were present. In the other case a woman with mitral stenosis, still under observation, developed prominent Q-waves in Leads II and III following an anginal attack. In another patient who came to autopsy, the coexistence of arteriosclerotic and rheumatic heart disease might have been suspected as the patient on fluoroscopy showed a large left auricle and right ventricle, not explained by hypertension alone. While some enlargement of the right heart and left auricle occurs in hypertensive heart failure, enlargement of the right side of the heart out of proportion to congestive failure should lead to suspicion of disease of the mitral valve.

The greatest and most significant reason for the very infrequent association of rheumatic and coronary disease is that rheumatic fever appears early in life and ordinarily runs its course before the usual period of degenerative heart disease. Rheumatic patients who live beyond middle life may develop coronary sclerosis and thrombosis. If they suffer from hypertension or diabetes mellitus, they will have the predisposition to coronary sclerosis which these diseases produce. The rheumatic process appears neither to predispose to nor to prevent degeneration of the coronary arteries.

In our series coronary sclerosis was encountered twice in patients under the age of forty years. In one patient, a woman twenty-nine years old, there was minimal atheromatosis; in the other, another female of twenty-nine years, coronary disease was significant, but she had suffered from marked hypertension. Several cases are very illuminating in showing the lack of relationship between one disease and the other. A woman of seventy-two years who died of leucemia (Case 15) at necropsy showed arteriosclerosis and calcification of both coronary arteries without narrowing. The mitral valve showed old lesions of the valves without deformity. The aortic valve showed sclerosis such as is frequently encountered in advanced age as part of generalized arteriosclerosis. A woman of ninety-one years (Case 26) at necropsy showed mitral stenosis and insufficiency and aortic insufficiency, with calcification of the aortic valves. The coronary arteries were diffusely calcified, with marked stenosis of the lumina.

In several instances of severe coronary sclerosis the associated rheumatic valvular lesions were insignificant and such as are frequently

found at necropsy of individuals dying of other diseases. Similarly, in several cases of advanced rheumatic valvular disease the coincidental arteriosclerotic lesions of the coronary arteries were of no significance. In still others neither the vascular nor the valvular lesion was of more than pathological interest, and the patient had presented neither history nor findings indicative of rheumatic heart disease or coronary arteriosclerosis. Cases may be cited of rheumatic subjects at or beyond middle life, in whom coronary disease corresponds roughly to the age of the individual.

SUMMARY

Coronary thrombosis is relatively rare in patients with rheumatic valvular disease. At necropsy the coronary arteries of young patients with rheumatic heart disease showed strikingly little arteriosclerotic change.

The age period of our series corresponds to that of ordinary cases of coronary sclerosis. In this material the degenerative changes of the coronary arteries corresponded roughly to the ages of the patients.

A rheumatic subject without aortic insufficiency or active carditis who develops anginal pain may have an independent coronary arteriosclerosis. On the other hand, a patient with arteriosclerotic heart disease who shows enlargement of the right heart or the left auricle out of proportion to congestive failure may have an associated rheumatic lesion of the mitral valve.

We believe that the most significant reason for the infrequent association of rheumatic and arteriosclerotic heart disease is that rheumatic fever runs its course before the degenerative period of heart disease. Those who survive middle life, especially if they develop hypertension or diabetes mellitus, may develop arteriosclerotic heart disease. Rheumatic fever per se does not, however, appear to predispose to coronary arteriosclerosis.

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THE ARM-TO-CAROTID CIRCULATION TIME IN PROLONGED THERAPEUTIC FEVER*

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THE importance of the velocity of the blood flow in the study of the dynamics of the cardiovascular system has already been demonstrated.¹ Determinations have been made on normal individuals at rest and during exercise,² on patients with cardiac and thyroid disorders,¹ hypertension,¹ emphysema,¹ and anemia,¹ and following an elevation of body metabolism by means of dinitrophenol.³ Observers have paid little attention to the effect of fever, infectious or artificial, upon the velocity of blood flow.

During the past five years the use of artificially induced therapeutic fever has increased considerably. Since this type of fever can be easily controlled, it affords an excellent opportunity to determine the effect of sustained fever upon the velocity of the blood flow.

The results of earlier experiments,⁴ during which body temperature was raised and immediately lowered, have shown that artificially induced fever causes an increase in the velocity of blood flow, most marked in electric blanket fever, less so in diathermy fever, and least in fever induced by intravenous typhoid vaccine. In addition it was seen that the increase in the velocity of blood flow during diathermy fever was much more marked in a patient with syphilitic heart disease than in a patient with an apparently normal heart.

Treatment by means of therapeutic fever in this clinic necessitates the prolongation of body temperature at a level above 104° F. (rectal) from three to five hours. Repeated determinations of the velocity of blood flow on a group of patients during the fastigium of fever would enable one to note: (a) the effect of sustained fever upon the velocity of blood flow; (b) the constancy or inconstancy of these changes for nearly similar body temperatures in the same patient; and (c) the relationship between changes in the velocity of flow and other clinical findings such as pulse rate, body temperature, systolic, diastolic, and pulse pressures.

MATERIAL

Determinations of the velocity of flow were made on fifteen male patients, varying from twenty-one to fifty-three years in age, who were given fever therapy for the following disorders:

6 patients with diagnosis of general paresis

2 patients with diagnosis of congenital syphilis with interstitial keratitis

*From the Neurosyphilis Clinic of the Boston Psychopathic Hospital under the direction of Dr. Harry C. Solomon, chief of therapeutic research.

- 2 patients with diagnosis of primary optic atrophy
- 1 patient with diagnosis of tabes with gastric crisis
- 1 patient with diagnosis of Wassermann-fast syphilis
- 1 patient with diagnosis of acute gonorrheal urethritis
- 1 patient with diagnosis of acute gonorrheal arthritis and urethritis
- 1 patient with diagnosis of multiple sclerosis.

One of the patients with general paresis revealed typical findings of rheumatic mitral stenosis; a second, hypotension, bradycardia, and diminished heart sounds.

METHODS

The sodium cyanide method of Robb and Weiss⁵ for the determination of the arm-to-carotid circulation time was used. From 0.55 c.c. to 0.8 c.c. of a 2 per cent solution of sodium cyanide was injected intravenously. In order to eliminate any possibility of error both the injection time and the respiratory response as obtained by means of a pneumograph were recorded on a smoked drum. A time recorder was also used, and the interval of time elapsing between the injection of the sodium cyanide into the veins at the elbow and the respiratory response was measured off and considered the arm-to-carotid circulation time. All determinations except when specified were made under basal conditions and without sedatives.

Fever was induced by means of the Kettering hypertherm,⁶ an air-conditioned cabinet of from 35 per cent to 45 per cent humidity and with a standardized air velocity. Dry bulb temperatures within the cabinet range from 150 to 160° F. and the wet bulb temperature from 125 to 130° F. The patient lies within the cabinet, covered with blankets and towels, the head protruding from the box and cooled by an electric fan.

On the morning of treatment no breakfast was given (unless noted otherwise). The patient was weighed, then he lay on the hypertherm bed for at least twenty minutes, following which pulse rate and blood pressure readings were obtained every three to five minutes for at least fifteen minutes. A velocity rate was then determined and in ten patients repeated. Fever treatment was then started, and body temperature was raised as rapidly as possible to the desired height, usually in about one and one-half hours. The hypertherm current was then turned off, and the patient wrapped in blankets to maintain the body temperature at levels of 104° to 106° F. (R) for three to five hours. Three to six velocity determinations were made during the fastigium of fever. Immediately preceding these determinations, pulse rate, blood pressure, and temperature readings were obtained. Fluids consisting of 0.6 per cent saline were given freely during the treatment, with the result that patients as a rule showed only a slight loss (0-2½ pounds) in weight and in some instances an increase (0-2 pounds) occurred. One patient (A. A.) showed a loss of 6 pounds as a result of treatment.

RESULTS AND DISCUSSION

Seventeen hypertherm treatments were given to fifteen patients during which velocity rates were determined before and during induced fever. In twelve patients the initial velocity rates (Table I) were normal,⁵ varying from 14 to 20½ seconds. In the remaining three patients (G. O., J. N., and D. T.) the velocity rates were slower than normal, 23, 26, and 35 to 41 seconds, respectively. The slow velocity time of patient G. O. is due, not to the presence of a rheumatic valvular lesion, but to early symptoms of myocardial insufficiency, palpitation and dyspnea of which he complained. Patient J. N. revealed no cardiac

pathology on examination, but because of a tabetic gastric crisis frequent vomiting occurred, with a resultant dehydration and an increase in the viscosity of the blood. This is probably responsible for the slow velocity time since the flow of a fluid in a tube is inversely proportional to the viscosity of the fluid (provided other factors remain equal), and it has already been shown¹ that in polycythemia the increase in blood viscosity is accompanied by a slowing of the circulation time. The rather marked slowing of the velocity of flow in patient D. T. is due to an impaired myocardium as seen from the findings of a hypotension, 87/64 mm. Hg, and feeble heart sounds.

TABLE I
VELOCITY RATES BEFORE FEVER INDUCTION

PATIENT	VELOCITY TIME (IN SECONDS)	PATIENT	VELOCITY TIME (IN SECONDS)
A. A.*	15 14	A. M.	17½ 19
R. St.*	16½ 15½ 14	S. M.	18½
R. S.	17 15	L. G.	19
J. P.	15½ 16½ 17½	J. M.	19½ 20½
F. K.	15½ 20½ 18	G. O.	23
B. C.*	15½ 20½	J. N.	26
J. Mg.	16 16½	D. T.	41 35
G. M.	17		

*Breakfast before treatment.

Duplicate initial velocity rates were obtained on ten patients and showed normal variations of 2 seconds or less in seven.⁵ In the remaining three patients (F. K., B. C., and D. T.) variations of 5, 5 and 6 seconds, respectively, occurred. The greater than normal variations occurring in patients F. K. and B. C. are probably due to the apprehension of both patients before fever induction; that of patient D. T. can be attributed to the very slow velocity time, the variations becoming greater as the slowing of the circulation time increases.

When the initial velocity rates of the group are taken as a whole, no relationship can be found between the velocity of flow and other clinical findings such as pulse rate, body temperature, systolic, diastolic, and pulse pressures.

TABLE II
VELOCITY RATES DURING PROLONGED HYPERTHYREXIA

PA-TIENT	AGE	DIAGNOSIS	TIME	B. P.	PULSE	TEMP. (F.)	VELOCITY (SEC.)	COMMENT
G. O.	47	General paresis	9:22	132/87	92	99.2	23	Rheumatic heart disease: mitral stenosis
			1:15	100/60	132	105.8	13½	
			2:45	100/64	134	105.0	14	
			3:22	98/56	144	105.6	13	
A. M.	44	General paresis	9:12	116/77	77	98.6	17½	
			9:18				19	
			11:32	136/ 0	129	105.6	10¼	
			12:17	128/ 0	129	105.6	10½	
			2:02	130/ 0	134	105.0	11	
			2:42	130/ 0	144	106.0	10½	
R. St.	29	Multiple sclerosis	10:05	113/90	74	98.4	16	Breakfast at 6:30 A.M.
			10:15				15	
			12:20	132/50	134	104.8	9	
			1:15	103/28	122	104.4	8½	
			2:00	124/40	140	105.0	9½	
			2:22	125/70	134	105.0	8½	
			9:03	123/89	72	99.2	14	
			11:20	140/50	124	105.0	9½	
			12:33	146/46	135	104.5	8½	
			1:32	120/60	144	104.0	10	
			2:28	122/40	144	103.6	8	
			3:29	100/25	147	104.8	11	
J. P.	40	Gonorrheal urethritis	9:01	103/69	64	97.6	15	
			9:12				16½	
			11:30	122/ 0	148	106.4	12	
			12:28	76/ 0	141	105.8	12	
			1:32	82/30	152	105.0	12	
			2:28	88/ 0	145	106.0	11	
			8:30	98/66	58	98.4	17½	
			12:50	96/40	135	104.0	13½	
			1:38	104/ 0	144	105.0	10½	
			2:08	108/10	148	105.6	12½	
			2:54	98/ 0	147	106.0	13	
			3:31	86/ 0	144	106.0	12	
G. M.	23	Congenital syphilis	9:20	117/49	71	99.0	17	
			12:32	150/ 0	112	105.0	9½	
		Interstitial keratitis	1:20	146/ 0	110	104.0	9½	
			1:55	140/ 0	117	103.6	10	
			2:50	138/ 0	110	103.4	10½	
R. S.	24	Wassermann-fast syphilis	10:56	130/76	87	98.0	17	
			11:00				15	
			1:40	110/60	125	104.8	16	
			1:45	110/60	125	104.8	14½	
			3:43	102/60	117	104.0	14	
F. K.	48	General paresis	9:11	115/75	85	99.0	15½	
			9:16	115/75	85	99.0	20½	
			9:22	115/75	85	99.0	18	
			11:18	142/60	144	105.6	10½	
			11:44	114/ 0	162	106.4	13	
			1:50	108/ 0	140	106.0	10½	
			2:11	104/ 0	165	106.2	11½	

TABLE II—CONT'D

PATIENT	AGE	DIAGNOSIS	TIME	B. P.	PULSE	TEMP. (F.)	VELOCITY (SEC.)	COMMENT
J. Mg.	27	Gonorrheal urethritis and arthritis	9:22	130/65	90	100.2	16	
			9:34				16½	
			11:12	125/ 0	140	105.0	8	
			12:01	124/ 0	129	105.0	9½	
			12:55	125/ 0	123	104.4	6½	
			1:15	125/ 0	124	104.0	10½	
J. M.	28	General paresis	9:40	97/54	73	99.0	19½	
			9:45				20½	
			11:55	130/ 0	156	105.2	7½	
			12:23	110/ 0	156	106.2	7½	
			1:23	114/ 0	146	105.6	10½	
			2:32	102/ 0	132	105.0	11	
			3:15	106/ 0	134	104.0	11½	
			3:20	106/ 0	134	104.0	8	
J. N.	37	Tabes dorsalis with gastric crisis	9:48	123/86	88	98.6	26	
			12:30	120/60	140	106.0	11½	
			1:15	120/56	140	105.8	11	
			2:30	90/40	128	105.0	16	
S. M.	36	General paresis	9:30	103/69	81	99.2	18½	
			11:37	100/58	120	106.2	8½	
			12:30	102/20	132	106.0	9	
			1:32	102/60	120	105.2	14	
			2:30	108/66	100	104.0	12	
D. T.	46	General paresis hypotension	9:45	87/64	52	98.6	41	Heart sounds of poor quality. Paraldehyde 8 c.c. at 10:00 A.M.
			9:55				35	
			11:55	128/76	122	106.0	13	
			1:25	110/74	120	106.2	14	
			1:57	106/70	124	105.8	11½	
			2:50	90/62	112	105.0	17½	
B. C.	21	Congenital syphilis Interstitial keratitis	10:05	125/77	87	100.0	15½	Patient had breakfast at 6:30 A.M.
			10:10				20½	
			12:16	132/ 0	112	105.6	9½	
			1:03	120/10	104	105.6	12½	
			1:50	112/30	108	104.8	11	
			2:48	106/ 0	114	104.4	15½	
L. G.	47	Primary optic atrophy	9:50	128/78	88	98.8	19	
			11:30	134/54	148	105.0	15½	
			12:18	115/60	138	105.0	18½	
			1:03	86/50	140	105.0	11½	
			1:37	90/50	140	104.8	14½	
A. A.	53	Primary optic atrophy	9:45	133/68	83	99.0	15	Cerebral thrombosis during treatment Breakfast at 6:30 A.M.
			9:50				14	
			11:43	120/ 0	148	106.0	8	
			12:28	106/ 0	162	107.2	12½	
			12:58	84/ 0	168	107.0	13½	
			1:50	78/44	132	105.8	14	
			2:32	84/ 0	120	106.0	15	
			3:13	110/44	120	106.0	7	

VELOCITY RATES DURING FEVER

Seventy-one velocity rates obtained during the prolongation of high body temperature during seventeen fever treatments showed, with but four exceptions, a hastening in the velocity of flow over that obtained

before the induction of fever (Table II). The four exceptions (one each in patients R. S. and B. C., two in patient A. A.) revealed velocity rates at a temperature of 104.4° to 106° F. which were equal to that obtained before the induction of fever. At no time was the circulation time during fever slower than that obtained at normal body temperature. The hastening of the circulation was accompanied by a more rapid pulse rate and in most cases by an increase in the pulse pressure, brought about as a rule, by a rise in the systolic and a marked fall in the diastolic level. The greatest shortening of the circulation time during sustained fever occurred in patient D. T., from 117 per cent to 225 per cent for a temperature of 105 to 106.2° F., accompanied by an increase of from 115 per cent to 138 per cent in the pulse rate. Patient J. P., who showed a nearly similar increase in the pulse rate (from 120 per cent to 155 per cent for a sustained temperature of 104 to 106.4° F.), revealed increases of only from 30 per cent to 67 per cent in the velocity time. The small-

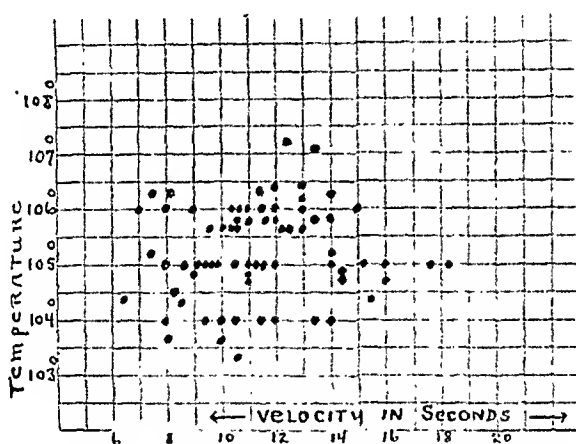


Fig. 1.—Velocity of flow as affected by body temperature.

est increase in the velocity time occurred in patient R. S.—from 0 to 13 per cent for a body temperature of 104 to 104.8° F. No definite relationship could be found in the individual patient between the velocity of flow during sustained fever and other clinical findings (body temperature, pulse rate, systolic, diastolic, and pulse pressures). When the results of the group are taken as a whole, variations in the velocity time as great as 11 seconds occurred for nearly similar body temperatures (Fig. 1). A suggestive linear relationship is seen best between the velocity time and the systolic blood pressure, less so between the velocity time and the pulse pressure (Fig. 2).

The results obtained during sustained fever can be divided roughly into two groups:

Group 1. Seven patients (G. O., A. M., R. St., J. P., G. M., R. S., F. K.) who showed a fairly constant velocity rate, individual variations of 3 seconds or less for body temperature fluctuations from 0.6 to 2° F. during nine fever treatments.

Group 2. The remaining eight patients (J. Mg., J. M., J. N., S. M., D. T., B. C., L. G., A. A.) who showed individual variations of from 4 to 8 seconds for body temperature fluctuations of 0.2 to 2.2° F. during eight fever treatments.

The differences between these two groups cannot be attributed to the more marked changes in other clinical findings (i.e., pulse rate, body

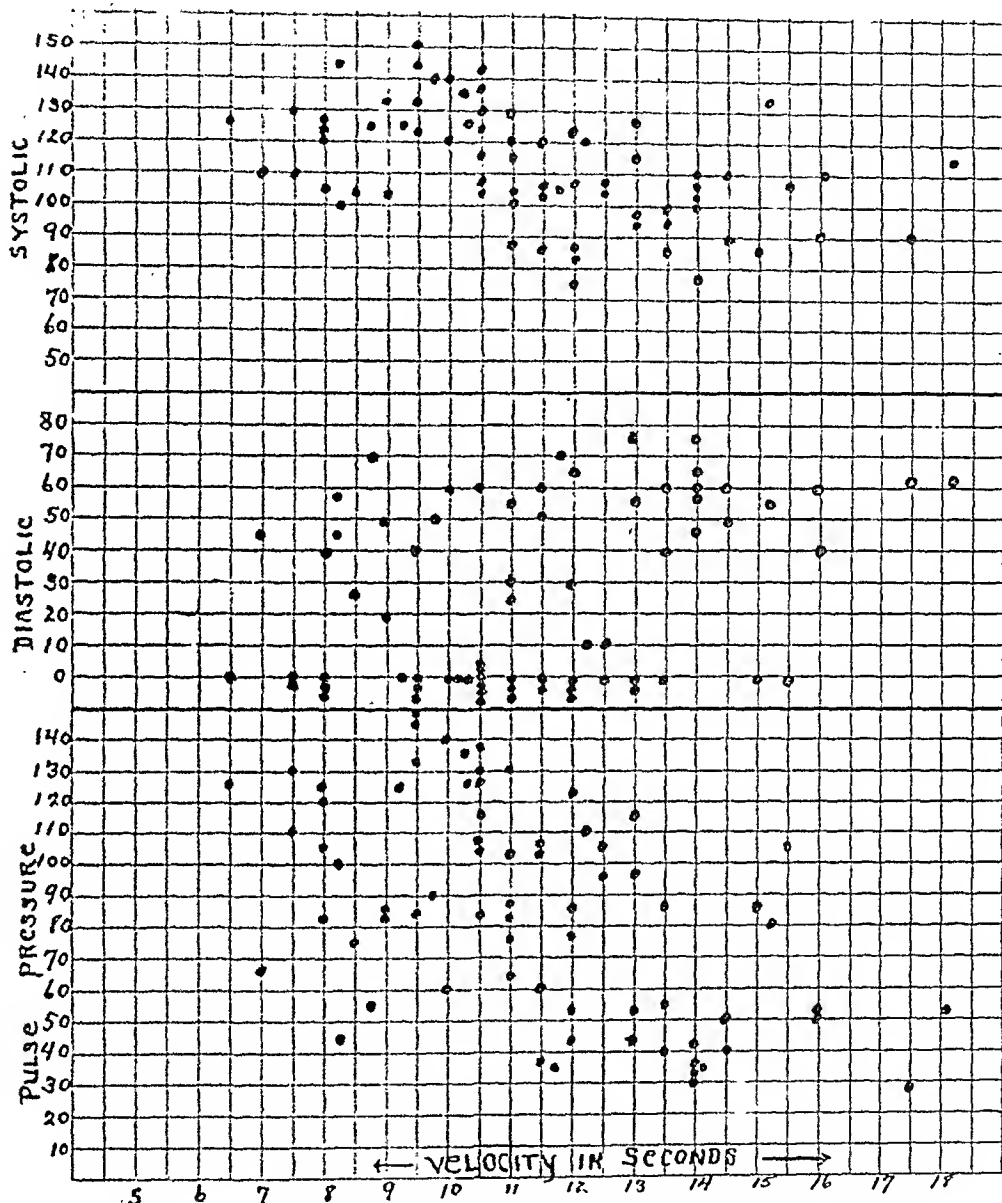


Fig. 2.—Velocity of flow during fever and the systolic, diastolic, and pulse pressures.

temperature, systolic, diastolic and pulse pressures) in one than in the other. It cannot be explained by the degree of restlessness or discomfort during fever, as seen from the results obtained in patients R. S. and B. C. Both patients exhibited a marked degree of restlessness and discomfort and yet the velocity rates in the former were fairly constant and in the latter revealed fluctuations as great as 6 seconds, the pulse rate, blood pressure and body temperature changes being slight and not accounting for the differences obtained.

With an increase in body temperature, such as occurs in artificial fever, body metabolism is increased⁷ and the blood flow to the tissues, with their greatly increased vascular bed, is hastened. The pulse rate and the pulse pressure, signifying as a rule a greater cardiac output, are increased. The venous pressure must increase in order to permit a greater return to the heart. Were all these changes, together with the blood volume, constant for a specific temperature, one would expect a fixed increase in the circulation time.

At fairly constant sustained temperature levels during artificial fever the increase in the metabolic rate is not fixed;⁷ the venous pressure shows fluctuations in both directions;⁸ the area of the vascular bed is not constant;⁹ and the plasma volume shows variable degrees of concentration.⁸ In addition, the pulse rate and the pulse pressures vary. Since all these factors show inconstant changes, the circulation time should do likewise, greater fluctuations in the velocity time occurring in those patients in whom these changes are more marked.

In patient A. A. no hastening of flow occurred on two occasions at temperatures of 105.8 and 106° F. This was accompanied by a marked drop in blood pressure from a level of 133/68 before treatment to 78/44 and 84/0, a forerunner of peripheral vascular shock brought on by exposure to hot moist air.⁸ The failure of the velocity of flow to be hastened at these high temperature levels, the marked drop in blood pressure, the reduction of the blood plasma volume which occurs⁸ (especially so in this patient in view of the loss of 6 pounds in body weight during treatment), all were of importance in the development in this patient of a cerebral thrombosis during treatment. With a subsequent rise in the systolic blood pressure a hastening of the blood flow occurred.

The velocity rates obtained during sustained fever reveal that no other clinical finding is indicative of the rapidity of the blood flow under these conditions. The pulse rate and blood pressure, which to some denote the state of the circulation, do not indicate the degree of fluctuation in the circulation time which may occur. This again emphasizes the importance of the velocity of blood flow as an index of cardiac effort under conditions of stress.

SUMMARY

Therapeutic fever was induced on seventeen occasions in fifteen male subjects by means of the Kettering hypertherm and the arm-to-carotid circulation time determined before and during the prolongation of high body temperature.

In twelve patients the initial velocity rates before fever induction were normal, ranging from 14 to 20½ seconds. In three patients the initial rates were below normal, 23 to 41 seconds, and are attributed in two patients to myocardial degeneration and in the third to increased viscosity of the blood as a result of repeated vomiting.

Seventy-one determinations of the circulation time at temperature levels of from 103.4 to 107.2° F. prolonged from three to five hours revealed a hastening of the velocity of the blood flow on all but four occasions. In the individual patient no definite relationship was found between the velocity of flow during sustained fever and the body temperature, pulse rate, systolic, diastolic or pulse pressures.

In seven patients the shortened circulation time during sustained fever was fairly constant, revealing fluctuations of 3 seconds or less for body temperature changes of 0.6 to 2° F. In the remaining eight patients variations of 4 to 8 seconds occurred for body temperature changes of 0.2 to 2.2° F.

The greater fluctuations in the circulation time in the second group are attributed to greater variations in concomitant phenomena during fever, among them the metabolic rate, venous pressure, plasma volume, and area of the vascular bed.

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LIGATION OF THE CORONARY ARTERIES IN JAVANESE MONKEYS*†

I. INTRODUCTION, GENERAL EXPERIMENTAL RESULTS, ESPECIALLY THE CHANGES IN THE VENTRICULAR ELECTROCARDIOGRAM

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THE problem of what changes take place in the electrocardiogram owing to local disturbances of the coronary circulation is of great interest both physiologically and clinically. The physiologist hopes to be able to extend his knowledge of the construction of a normal electrocardiogram by comparative studies of these changes, looking in his experiments for a relationship between definite changes in the electrical curves and functional disturbances in definite parts of the heart. As has been mentioned by Lewis,¹ "the cutting out of large areas of the musculature by obstructing the blood supply should ultimately prove of value in arriving at conclusions as to the manner in which the normal electrocardiogram is produced." The clinician hopes that electrocardiographic changes will be of value in diagnosis, and in studying the course of diseases and the results of his treatment in patients with disturbances of the coronary circulation and heart muscle function.

Although extensive work has been carried out on this subject both experimentally and clinically and is still being carried out daily (see for general information, among others, Condorelli,² Hoehrein,³ Lian⁴ and Hyman and Parsonnet⁵), we were of the opinion that an experimental investigation in monkeys might contribute to our knowledge; the more so since, as far as we know, it had never yet been made.

This article describes the results of experiments which we have been conducting since 1933 on the Javanese monkey, *Macaca irus* (nomenclature of Hartman and Straus,⁶ formerly called *Cynomolgus*).

For experimental electrocardiographic researches, especially when it is desired to apply the results of the experiments to human physiology and clinical medicine, monkeys take the first place among all experimental animals. As has been shown in previous papers⁷ and is reproduced in Fig. 1, the monkey heart has great similarities both anatomically and physiologically with the human heart, especially as far as the internal structure, the position in the thorax, and the fixation through adhesions of the pericardium to the diaphragm are concerned. These factors are of great importance in determining the form of the electrocardiogram, which we have found in practice to show a far

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more constant configuration in *Macaca* than, for instance, in dogs. Changes in the form of the electrocardiogram are not so easily caused in monkeys as in other animals by changes in position of the heart and may, therefore, with far greater certainty be attributed to changes in the function of that organ. In our opinion, then, it is quite correct that warnings should be appearing in ever increasing number against applying to man results and data obtained by experiments on dogs.^{8, 9, 10}

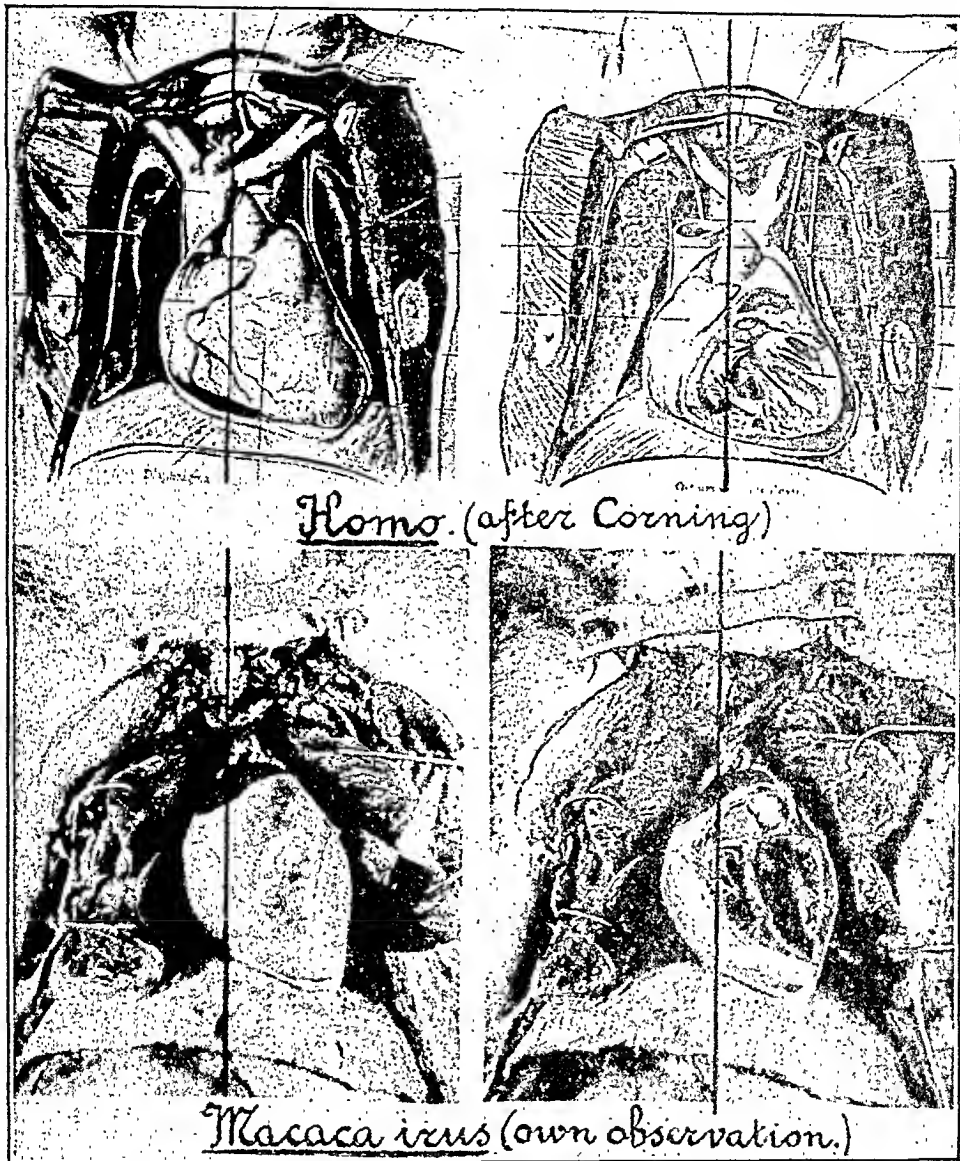


Fig. 1.—See text.

We were disappointed in our expectation that the monkey, or at any rate *Macaca irus*, in addition to structure, position, and fixation of the heart, would also show great similarity to man in the anatomical relationships of the coronary arteries. We found that in the great majority of these monkeys the ramus descendens posterior was a branch of the left coronary artery, a condition found in only from 10 to 20 per cent of hearts in man.^{2*}

*In the anthropoid apes, among others the Hylobates, we thus far have found the ramus descendens posterior without exception branching from the right coronary artery. These animals approximate man most closely, and in all probability also in the structure of their coronary system.

When in fresh *Macaca irus* hearts the orifices of the coronary arteries in the sinus of Valsalva are observed, the left artery usually gives the impression of being larger in diameter than the right, whereas in man the opposite is usually the case.¹¹ With the aid of sounds of known diameter an approximate measurement was made of the diameter of the orifices of the coronary arteries in nineteen fresh *Macaca* hearts. In fifteen of these hearts the left artery was definitely larger in diameter than the right, while in the other four the diameters of the right and left artery were the same. The average diameter of the left arteries was 1.60 mm., that of the right arteries was 1.26 mm.

In direct agreement with this result we found by experiments with isolated *Macaca irus* hearts, prepared according to the method of Langendorff, that ligation of the left artery reduced the coronary flow more than ligation of the right artery. The areas supplied by the arteries were determined in another twenty of these monkeys by in-

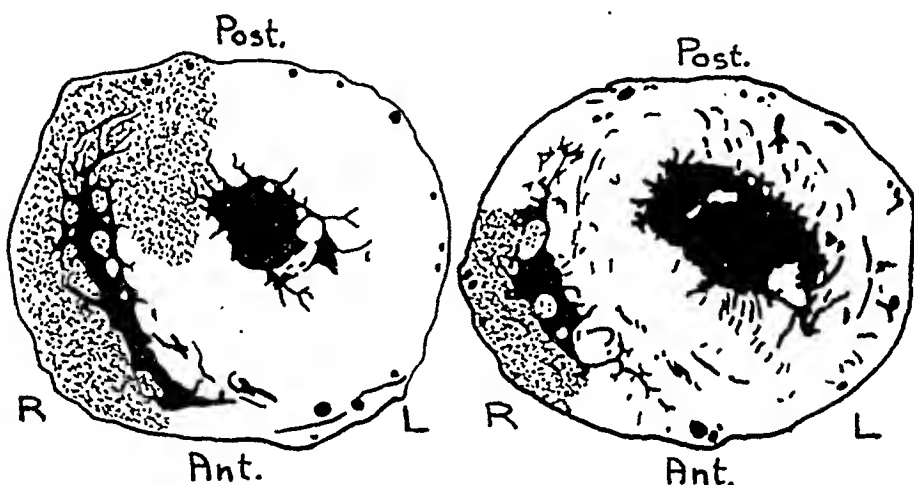


Fig. 2.—Areas of ventricular wall and septum, supplied by right and left artery, respectively, in *Macaca*. The degree of preponderance of the left artery differs in various specimens. Two types are shown. Both hearts were cut through the middle, perpendicularly to the axis.

jection of earmine gelatin and Berlin blue gelatin through the orifices, after the method of Romeis.¹² The result we usually obtained is shown in Fig. 2.

In *Macaca irus* the following distribution is seen: *Left coronary artery*: left auricle and auricular appendix; the whole wall of the left ventricle, anterior and posterior; sometimes the whole septum, sometimes only the anterior two-thirds of the septum; often the lower apical portion of the anterior surface of the right ventricle and a strip of the right ventricle along the sulcus longitudinalis anterior; all the papillary muscles and the trabeculae on the left side and the anterior papillary muscles and trabeculae on the right side. *Right coronary artery*: right auricle and auricular appendix; the interauricular septum; the region around the sinus node; the whole lateral and posterior wall of the right ventricle; often the posterior one-third of the interventricular septum; the anterior wall of the right ventricle with the exception of a strip along the sulcus longitudinalis anterior; and the posterior papillary muscles and trabeculae on the right. Individual variations were observed, especially where the blood supply of the septum was concerned.

In the relationships of the coronary arteries, therefore, *Macaca irus* shows a certain resemblance to the dog.² We merely call attention to this fact, but the relations mentioned do not, in our opinion, offer any objection to using these monkeys for seeking a possible connection between changes in the electrocardiogram and a possible area of disturbed function eventually to be localized macro- and microscopically since we may expect that as far as the electrocardiogram is concerned, the localization of the lesion is determinative, independently of whether the lesion was caused by a disturbance of the left or right artery.¹³ For example, it would make no difference to the electrocardiographic results of a bundle-branch section whether that section were made with the right or with the left hand! For electrocardiographic studies the *Macaca* heart, because of its more human architecture, position and fixation, and, as was recently pointed out, also the more human form of the *Macaca* thorax,¹⁴ will maintain its advantages for physiology and clinical medicine even though the coronary distribution is somewhat different from that in man.

Coronary ligations have been attempted but seldom in monkeys. Hirsch¹⁵ ligated the ramus descendens anterior of the left coronary artery in two monkeys (species not mentioned) and observed no permanent change in the heart action; there appeared a temporary arrhythmia. No records were made; the experiment was principally carried out to obtain further insight into the question whether the coronary arteries anatomically or functionally must be regarded as end-arteries. Spalteholz found in these monkeys *myomalacische Schwiehlen*, but his illustrations¹⁵ refer only to dog hearts.

We have found in the literature only two additional reports of experimental research on the coronary arteries in monkeys. Sutton and Lüeth¹⁶ in their attempts to produce experimentally pain by operative interference on the heart and vessels of dogs used "as a check" one monkey (*Macaca*?). They opened its thorax under local anesthesia and clamped off one of the coronary branches. According to their report, the dimensions of the heart were too small for them to be able to carry out their original plan and ligate the artery. Barbour and Prince¹⁷ studied the effect of epinephrine on the coronary circulation of isolated hearts of the *Macaca rhesus*.

In none of these publications was any mention made of electrocardiographic investigations.

We shall now discuss our experiments and the results we obtained in monkeys of the *Macaca irus* variety, one of the common Java monkeys, weighing between 3 and 7 kilograms.

In these experiments we limited ourselves to the ligation of the *ramus descendens anterior of the left coronary artery*, about 2 to 3 mm. distal to the origin of the ramus circumflexus, and the ligation of the

principal stem of the right coronary artery, about 5 mm. distal to its origin from the aorta, in the auriculoventricular groove below the right auricular appendix.

These customary ligation sites are shown in the accompanying diagram (Fig. 3).

Technic.—For the details of the technic used by us in making electrocardiograms of monkeys either in three leads simultaneously or successively, and also for certain physiological peculiarities of monkey hearts,* we refer to former publications.⁷ Particular attention was paid to avoiding technical errors, since, especially in the monkey heart with its rapid action, they might readily lead to distorted records.

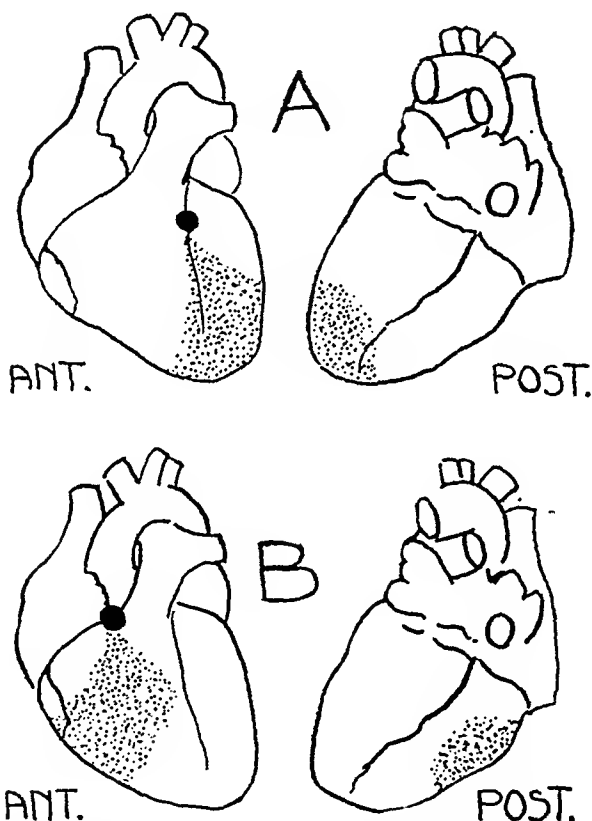


Fig. 3.—Usual site of ligation of the ramus descendens anterior and of right artery, and areas which showed obstructed circulation in injected preparations.

We assured ourselves that we could rely entirely on our curves, made as they were with high registration speed by the latest model of Cambridge galvanometers at a projection distance of 120 cm. In our experience the so-called "modern" electrocardiographs are often unable to record accurate curves at heart frequencies such as occur in monkeys. We used, before passing on to coronary ligation in the remaining monkeys, fifteen monkeys solely and especially to investigate the effects on the electrocardiogram of various factors such as narcosis, opening the trachea, artificial respiration, opening the thorax, pneumothorax, opening the pericardium, exposing the heart, wounding the heart without coronary ligation, changes in body position, asphyxia, and so forth. Many observers^{9, 18, 19, 20} have quite correctly called atten-

*The pulse rate average in these monkeys is 225 per minute; the P-R interval about 0.07 sec.; the QRS complex about 0.03 sec.; systole lasts somewhat longer than diastole.

tion to the fact that such factors might well lead to distortions in the electrocardiogram. It is our experience, however, that they may be left out of consideration as causes of distortion if the following operative technic be used in the ligation:

After the animal has been placed on its back and connected to the electrodes in the manner earlier described⁷ and after the skin of the thorax has been shaved and sterilized by the application of tincture of iodine, as a narcotic, pernocton, 0.3 c.c. of a 10 per cent solution, or eripan sodium, 0.2 c.c. of a 10 per cent solution per kilogram of animal weight is injected intravenously very slowly. Then the trachea is opened and connected to a Palmer respiration apparatus driven by direct current; the skin and subcutaneous tissues are then cut through, on the left for access to the left coronary artery, on the right for the right coronary, and in both cases close to the sternum. The ribs from the second to the fifth are then cut through close to the sternum, care being taken to avoid the internal mammary artery, which should be ligated if it is accidentally cut. The thorax is then pressed open with a self-retaining wound retractor and the lung protected by gauze soaked in physiological saline. The pericardium is next opened and the flaps are turned back and fixed by hemostatic forceps so that the heart is left quietly beating in the pericardial bed. A ligature of silk or catgut is then passed around the artery desired by means of a very fine curved needle and the vessel is then tied off. The pericardium is sutured by catgut. The thoracic wound is then closed layer by layer while, the animal being disconnected from the respiration apparatus, the operator by carefully blowing up the lungs can be sure that no pneumothorax will follow. The skin wound is closed by metallic skin clips and gauze painted with a mastic solution. The tracheal cannula is then removed and the tracheal wound closed. We have found that if no ventricular fibrillation develops the animals breathe spontaneously at once and awaken from the narcosis in from one-half to one hour and that they are at once lively, take food, and as a rule show no signs of suffering any pain.

We shall consider exclusively results from successful experimental ligations, by which we mean: 1. Completely satisfactory course of both narcosis and operation with no significant postoperative rise or fall of body temperature, no significant hemorrhage, no pneumothorax, and no infection; 2. An actual closing off of the artery desired, controlled post mortem both macroscopically and microscopically.

In these small hearts beating with high frequency it is often practically impossible to ligate the arterial branch desired without including in the ligature one or more of the accompanying veins, which often lie superficial to the artery. This happened several times, but, according to others,^{9, 10, 21} it does not affect the results of ligation experiments in any material way. The microscopic examination showed that quite often small nerve fibers were also included in the ligature. We attach practically no significance to these accidental ligations since the obstruction of the coronary arteries from within by lycopodium, by which the nerves are spared, gives results similar to closing them off from without, at least in dogs¹⁰; damage to the outer side of the vessels in *Macaca* left no definite electrocardiographic changes after the circulation had been restored (see the clamping experiment described in Part III of this paper), and air embolism is capable of producing comparable changes (Fig. 17). We believe, however, that it is possible that these nerve ligations may be responsible for the fact that our monkeys, as a rule, showed no signs of pain. In this we agree with Sutton and Lueth.¹⁶

If we designate our animals by the numbers they bear in the collections of laboratory specimens, and further mark those monkeys in which the ligation of the ramus descendens anterior was applied with

TABLE I
SEE TEXT

MONKEY	DATE OF OPERATION	S-T DEVIATION AFTER OPERATION			SURVIVAL AFTER OPERATION	CAUSE OF DEATH*	REMARKS
		FIRST REG.	MAXIMUM	DISAPPEARED			
4 L	3/21/33	5 min. (A)	± 2 hr.	± 1 wk.	6 mo.	Killed	First S-T deviation Type A, after ±5 months other Type B. See text.
5 L	3/22/33	± 5 mo. (B)	± 6 mo.	?	36 min.	Fibrillation	
9 L	4/12/33	20 min.	?	?	5½ mo.	Killed	
13 L	5/13/33	3 min.	± 2 hr.	± 5 mo.	23 min.	Fibrillation	Fibrillation occurred before thorax was closed.
15 L	6/20/33	8 min.	> 29 min.	?	33 min.	Fibrillation	Deviation still increasing when fibrillation occurred.
16 L	6/21/33	2 min.	?	?	13 min.	Fibrillation	Bundle-branch block. See text.
17 L	10/18/33	± 4 min.	51 min.	± 1 day	2 days	?	Probable cardiac failure.
19 L	10/24/33	± 2 min.	64 min.	± 2 wk.	2 mo.	Fibrillation	Small amount of chloroform. See text.
26 L	11/28/33	?	?	?	27 min.	Fibrillation	Fibrillation at first registration after operation.
35 L	3/9/34	13 min.	56 min.	± 6 hr.	2 mo.	Killed	
44 L	3/20/34	9 min.	± 1½ hr.	± 1½ mo.	1½ mo.	Killed	Small deviation still present at death.
49 L	4/18/34	22 min.	68 min.	± 5 days	5 days	Fibrillation	Small deviation just before fibrillation.
51 L	5/9/34	± 20 min.	28 min.	± 1 mo.	± 1 mo.	Killed	Small deviation still present at death.
52 L	5/1/34	13 min.	> 16 min.	?	16 min.	Fibrillation	Deviation still increasing when fibrillation occurred.
53 L	5/25/34	18 min.	± 6 days	± 1 mo.	1 mo.	Killed	Small deviation still present at death.
AG L	4/5/35	± 8 min.	?	?	± 1 hr.	Killed	Temporarily closed, metal clip. See text.
6 L	3/28/33	1 min.	± 55 min.	± 7 wk.	7 wk.	?	{ Died 7 weeks after L., some hours after secondary
6 L+R	5/17/33	± 20 min.	± 64 min.	?	?	?	{ ligation of R. Probably no fibrillation. See text.
10 R	4/20/33	2 min.	58 min.	± 5 mo.	6 mo.	Killed	
11 R	4/21/33	15 min.	± 40 min.	± 1 day	6 mo.	Killed	
12 R	5/3/33	3 min.	± 63 min.	± 1 day	5½ mo.	Killed	
14 R	6/14/33	-	-	-	4 mo.	Killed	
23 R	11/12/33	2 min.	± 49 min.	?	6 hr.	?	No S-T deviation. See text.
25 R	11/24/33	4 min.	> 9 min.	?	1 hr.	?	Heart failure? Fibrillation not impossible.
31 R	1/13/34	-	-	-	1 mo.	Killed	No fibrillation. See text.
36 R	3/2/34	22 min.	± 1 hr.	?	6 hr.	?	No distinct S-T deviation. See text.
37 R	3/6/34	15 min.	± 43 min.	?	1 hr.	?	Probable fibrillation.
40 R	3/26/34	10 min.	?	?	35 min.	Fibrillation	No fibrillation. See text.
41 R	3/13/34	7 min.	± 57 min.	± 1 day	4 days	?	Fibrillation not excluded. See text.
43 R	3/20/34	15 min.	75 min.	± 12 days	1½ mo.	Killed	
56 R	5/15/34	20 min.	± 2 hr.	± wk.	3 wk.	Killed	
X R	3/11/34	± 5 min.	?	?	25 min.	Fibrillation	Vagi cut. See text.

*Killing was done by rapid intravenous injection of 6 to 8 c.c. of picrotoxin or cyan potassium.

an "L" and those in which the right artery was ligated with an "R," we obtain the following summary of our experimental material (Table I).

In total, therefore, we include in this report thirty-one monkeys. In seventeen of these animals the left ligation was applied and in fourteen the right. In one monkey (No. 6) first the left ligation was employed, and after seven weeks at a second operation the right ligation was made.

Electrocardiograms of each monkey (with the animal always in the same body position, horizontal and lying on its back) were made before the narcosis, during the narcosis, during various phases of the operation, and at various times after the operation. Records were made of the three classical leads, sometimes successively, but usually simultaneously.* We soon stopped making records during the operations while the thorax was still open as there were too many possible sources of error introduced.^{1, 10, 22, 23}

We observed various changes, especially in the ventricular electrocardiogram, and, further, arrhythmias, either accompanied by disturbances of conduction or not, such as extrasystoles, paroxysmal tachycardia, ventricular fibrillation, auriculoventricular block, delayed intraventricular conduction, bundle-branch block and nodal rhythm, all of which will be discussed below.

CHANGES IN THE VENTRICULAR ELECTROCARDIOGRAM

These can be divided into early (primary) changes and late (secondary) changes.

Among the former a definite displacement of the S-T segment, which in normal monkeys is isoelectric, was the most striking. This S-T deviation was found in all but two of the "left monkeys" (13 L and 26 L) and all but two of the "right monkeys" (14 R and 31 R). This was easily explained in the case of the two left monkeys since even by the time of the first recording after closing the thorax they both showed ventricular fibrillation. In the case of the two right monkeys it is probably connected with the peculiar position and size of the heart lesion which will be further discussed later.

We did not observe a similar rapid displacement of the S-T segment even in severe operations, unless a coronary artery was ligated. It was not caused by the thorax operation as such. This fact is illustrated by Fig. 4.

Calculated from the moment of ligation, the time at which the S-T deviation was first observed, at which it reached its maximum, and at which it disappeared (as far as the subsequent duration of life of

*In the curves reproduced, the three leads which were taken successively are separated by black horizontal lines; those not marked in this way are all simultaneous recordings. Sometimes, to save room for reproduction, the blank spaces between curves were partly cut away, identical phases again being placed in their original time relation to each other. Reprints of the original curves will be sent on request. The time is, as a rule, marked in $\frac{1}{2}$ and $\frac{1}{50}$ sec., sometimes also in $\frac{1}{10}$ sec.; 10 scale divisions represent 1 millivolt.

the animal allowed us to observe this latter point) will be found in Table I. It will be seen that, except in the special Case B of Monkey 4 L, the beginning of the deviation was registered on an average of about ten minutes after the ligation; however, it was often registered sooner, sometimes after only one or two minutes. In general the condition developed so rapidly that, practically speaking, a trained eye could see the typical changes in movement of the string even before the thorax was closed, and thus we knew that the ligation had been a success. Since we usually waited to make our first record after the operation until the thorax had at least been provisionally closed, the actual moment at which this phenomenon began, certainly should have fallen below the above mentioned average. This is in accordance with the observations of Wood and Wolferth¹⁹ in dogs.

In as far as it was possible to determine, the maximum S-T deviation was reached in an average of sixty-three minutes (excluding cases

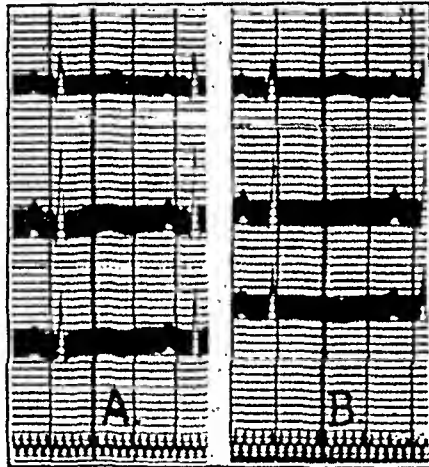


Fig. 4.—Control animal, Monkey 34, Leads I, II, and III. A, before operation; B, 2 hours after complete operation for ligation of the ramus descendens anterior, in which the ligature, as was found microscopically, missed the artery and included only fat. No change in electrical curve. No S-T displacement. Time marked in $\frac{1}{50}$ and $\frac{1}{100}$ sec.

4 L (B) and 53 L); it was practically never seen under twenty-eight minutes after the operation. The time within which the S-T segment again became isoelectric varied greatly. In our observations the minimum time was six hours and the maximum about five months after the operation, with an average of about one month. This time relationship must be considered of importance for a possible explanation of the deviation, which will be discussed in Part III of this paper.

A preliminary, but incomplete, impression of the deviations which occurred in our experiments may be obtained by observing only the upward or downward displacements without regarding the magnitudes of these displacements. If an S-T movement upward is indicated with \uparrow and one downward with \downarrow and an isoelectric state of the S-T segment with $=$, Table II will show the S-T displacements we observed in our monkeys.

At first glance it seems that greater regularity occurs in the cases of right ligation. The S-T deviation in the right monkeys was never upward in Lead I, but in almost all cases downward, while in Lead III the deviation was almost always upward. The deviation in Lead II was about equally often concordant with that in Lead I as with that in Lead III so that Lead II, contrary to reports of other investigators,¹³ in itself cannot be a guide for the type of curve.

There is seemingly less regularity in the results of the left ligation although S-T is more often deviated upward than downward in Lead I and the opposite holds good for Lead III. S-T in Lead II, as a rule, took the same direction as in Lead III even when in Lead I it was diverted upward and in Lead III downward.

TABLE II
DISPLACEMENTS OF S-T SEGMENT AS FOUND IN THE THREE LEADS
(SEE ALSO TEXT)

LEFT (ram. desc. anterior).

	4a	4b	5	6	9	15	16	17	19	35	44	49	51	52	53	RG
I	↓	↑	↑	↓	↑	=	↓	↑	↓	=	↑	↑	=	↓	↑	↑
II	↓	↑	↓	↑	↑	↑	↑	↓	↑	↓	↓	↓	↑	↓	↓	↑
III	↓	↓	↓	↑	↑	↑	↑	↓	↑	↓	↓	↓	↑	↓	↓	↓

RIGHT (art. con. dextra).

	10	11	12	23a	23b	25	36	37	40	41	43	56	X
I	↓	=	↓	↓	↓	↓	↓	↓	↓	↓	↓	=	↓
II	↑	↑	↓	↓	=	↓	↓	↓	↑	↓	=	↑	↑
III	↑	↑	↑	↑	↑	↓	↑	↑	↑	↑	↑	↑	↑

L+R art. con. dextra
7 weeks after ram.
desc. ant.

	6
I	↓
II	↓
III	↑

In accordance with the rule of Einthoven ($II - I = III$), which is applicable to all types of curves, an S-T deviation must always appear in at least two leads. Further, according to the scheme of the equilateral triangle^{18, 24, 25} which may also be applied to the monkey as has been shown before,⁷ a displacement in a certain direction and of a certain magnitude in any one lead can have a very widely divergent significance, depending on the displacement observed at the same time in the other leads. For instance, it is a very incomplete definition of such an S-T deviation to say only that it was directed upward in Lead I. All electrical potential differences the direction of which in the heart makes an angle with the horizontal varying from $+90^\circ$ through 0° to -90° could give such a deviation so that, as far as electrical relationships are concerned, cases showing such S-T deviation could differ by almost 180° from one another. The same applies to cases in which, for instance, an upward displacement in Lead III occurs. Potential

differences in the heart both from $+30^\circ$ to $+90^\circ$ left and from $+90^\circ$ via 180° to -150° right could give such changes in Lead III. Here, too, there is a play of about 180 degrees.

It will be clear, therefore, that the study of the S-T deviation in only one lead, as sometimes found in literature,^{26, 27, 28} cannot be regarded as complete. It is advisable to consider this phenomenon in at least two of the three leads *quantitatively*.

We may try to determine in that connection both the direction and the magnitude of the potential differences existing in the heart during the tracing of the S-T deviation. We shall not discuss in this article the manifest magnitude at maximum development although a study of the possible relation between it and the size and place of the heart lesions induced would undoubtedly be justified.

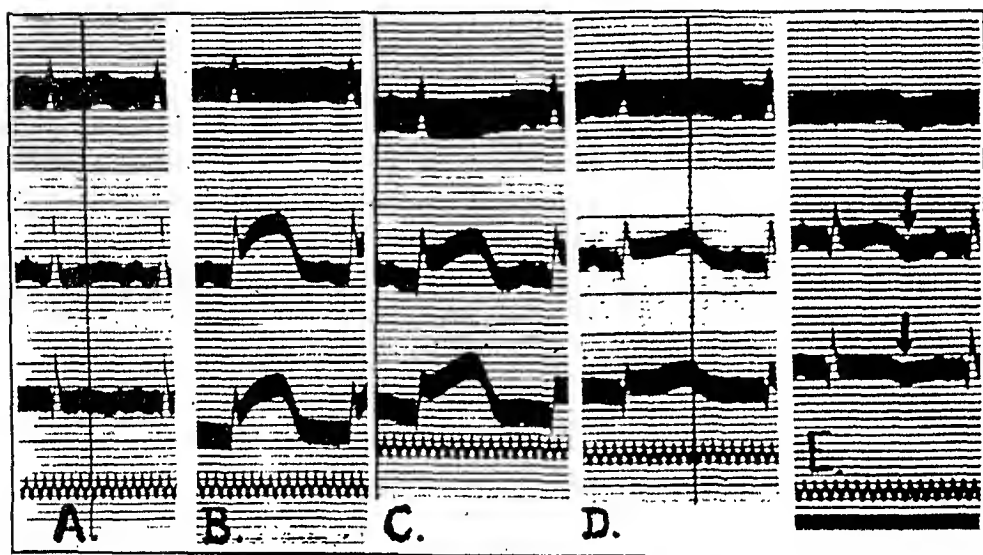


Fig. 5.—Monkey 51 L. A, before operation; B, 28 min., C, 33 min., D, 108 min., and E, 33 days after ligation of the ramus descendens anterior.

For the moment we shall limit ourselves to determining *the direction*.

Pardee²⁹ once suggested the possibility of a directional S-T displacement after coronary obstruction; Wilson and his associates³⁰ studied a possible direction and magnitude in semidirect leads after burning a part of the heart; however, both made, as far as we know, no quantitative measurements.

The direction of the manifest potential difference in the heart may be determined at any chosen part of the S-T deviation, as well as at any chosen part of a normal electrocardiogram.¹⁸ In many curves, indeed, for measuring the direction of the deviation, it is immaterial what series of synchronous points of the S-T segment are taken. For instance it will be seen from Fig. 5 that during the entire course of the S-T segment the electrical axis is directed perpendicularly to Lead I ($+90^\circ$).

For reasons that will be discussed later, we have limited ourselves to measuring the direction of the electrical S-T axis existing at the point of the beginning of the S-T deviation in a given complex, and, as will be described later in detail, as far as possible, at that time after the operation at which the deviation had reached its maximum development. Heretofore the S-T displacement was measured at the point at which the S-T segment springs from the QRS complex, or, if in our opinion the measurement could thereby be made more accurately, a point as near it as possible. In order to reduce errors of measurement to a minimum the direction was determined from the two leads in which the deviation was largest.

Table III gives the results of the measurements, constructions and calculations expressed as angle α of the triangle scheme, which, as has already been said above, is applicable to the monkey.

TABLE III

DIRECTION OF THE ELECTRICAL S-T AXIS IN DIFFERENT MONKEYS AFTER LEFT (L) AND RIGHT (R) LIGATION

MONKEY	CURVE NUMBER	DEVIATION IN MM.			ANGLE α	
		I	II	III	CONSTRUCTED	CALCULATED
4 L A	80	(- 5.9)	-12.8	- 6.9	-118°	-117°
B	142	+ 1.9	+ 1.1	(- 0.8)	+ 5°	+ 5°
5 L	171	+ 5.0	(- 1.9)	- 6.9	- 46°	- 45°
6 L	182	- 1.5	(+ 1.0)	+ 2.5	+127°	+127°
6 L+R	213	- 1.8	- 1.5	(+ 0.3)	-160°	-160°
9 L	276	+ 1.2	+ 2.4	(+ 1.2)	+ 60°	+ 60°
15 L	536	=	+ 6.0	+ 6.0	+ 90°	+ 90°
16 L	543	(- 0.4)	+ 2.1	+ 2.5	+ 98°	+ 99°
17 L	558	+ 1.9	(- 1.0)	- 2.9	- 51°	- 50°
19 L	620	(- 1.3)	+ 6.2	+ 7.5	+100°	+ 99°
35 L	1027	=	- 5.0	- 5.0	- 90°	- 90°
44 L	1094	+ 1.0	(- 0.5)	- 1.5	- 49°	- 49°
49 L	1140	+ 3.0	(- 0.6)	- 3.6	- 39°	- 39°
51 L	1164	=	+ 3.4	+ 3.4	+ 90°	+ 90°
52 L	1188	- 1.0	- 1.5	(- 0.5)	-131°	-131°
53 L	1199	(+ 0.5)	- 0.5	- 1.0	- 60°	- 60°
AG L	AG B	+ 7.6	(+ 3.5)	- 4.1	- 3°	- 3°
10 R	343	(- 4.7)	+ 5.5	+10.2	+117°	+117°
11 R	410	=	+ 1.0	+ 1.0	+ 90°	+ 90°
12 R	443	- 1.6	(- 0.6)	+ 1.0	+172°	+172°
23 R A	722	- 5.5	(- 1.0)	+ 4.5	+157°	+160°
B	728	- 5.0	=	+ 5.0	+150°	+150°
25 R	752	- 2.0	- 2.5	(- 0.5)	-140°	-139°
36 R	935	- 3.0	- 1.5	(+ 1.5)	+180°	+180°
37 R	947	- 1.5	(- 0.5)	+ 1.0	+169°	+169°
40 R	981	- 1.0	(+ 1.0)	+ 2.0	+120°	+120°
41 R	986	- 2.4	- 1.9	(+ 0.5)	-161°	-161°
43 R	1074	- 1.2	=	+ 1.2	+150°	+150°
56 R	1218	=	+ 1.0	+ 1.0	+ 90°	+ 90°
X R	1240	- 1.6	(+ 1.1)	+ 2.7	+127°	+126°

In composing this table, construction was carried out before the results of the calculations were known, by pointing off the measurements (c.q., multiplied 5, 10, or 20 times) on a schema similar to that described by Carter, Richter, and Greene.³¹ Calculations were made, using the table of Einthoven, Bergansius, and Bytel.³² This latter is more accurate, but more time consuming. As shown in our table, the errors

made by construction are very small, and in our opinion, for practical purposes including clinical use, insignificant. The measurements were made on the curves enlarged fifteen times by projection. In each lead in three successive complexes the distance of the origin of the S-T segment from the diastolic line was measured three times. In the table the number for each lead in this way represents the average of nine measurements. For practical purposes measurements with a magnifying glass would be sufficient in many cases. In order to reduce errors of measurements to a minimum, those two leads in which the deviation was greatest were selected. For each monkey, for the same reason, those curves were taken in which the deviation was, as far as possible, at its maximum development. The numbers in parentheses were not actually measured, but calculated according to Einthoven's rule.

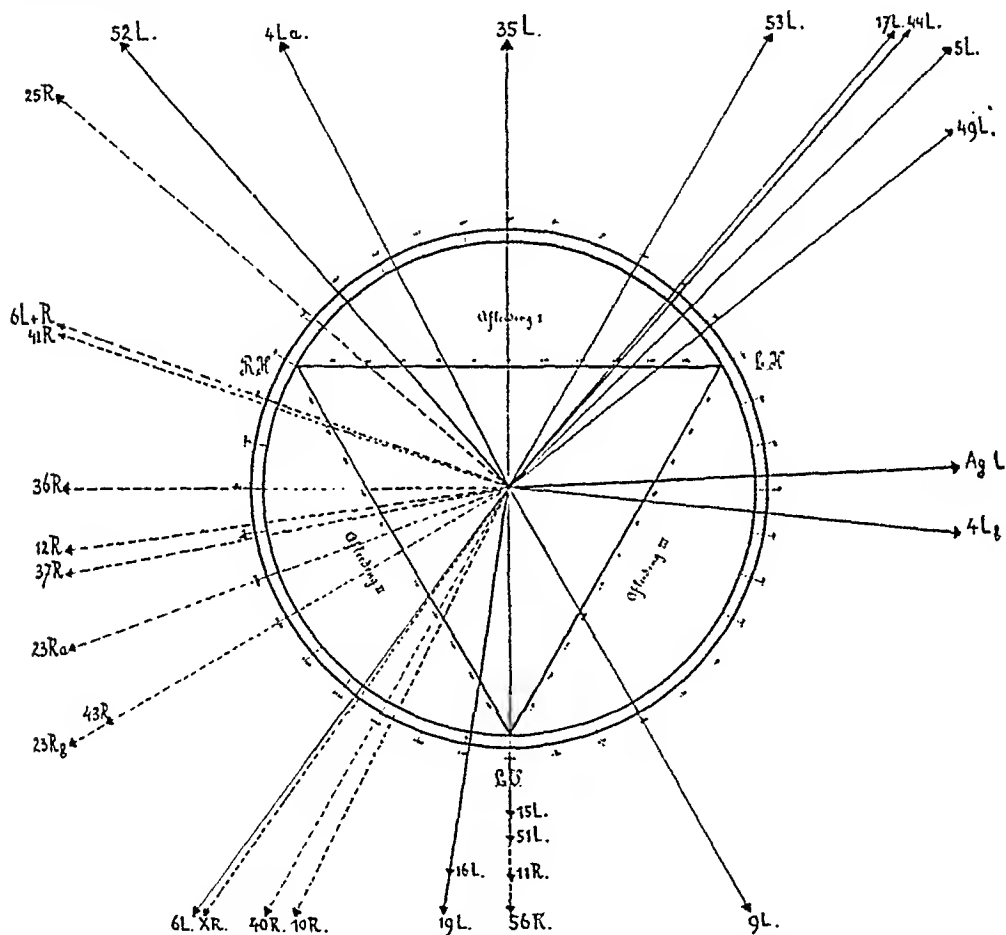


Fig. 6.—Direction of the electrical ST axis in different monkeys after ligation of the ramus descendens anterior (—) and of right coronary artery (---). Further details in text.

The results are also recorded in Fig. 6 in which the numbers of the monkeys concerned are also given with "L" and "R" to designate whether the ligation was left or right.

From Fig. 6 it will be seen that the S-T axes in cases of right and left ligations overlap only in a very small area (the sector from $+90^\circ$ to $+127^\circ$) while over the entire remaining area each takes its own field, the right monkeys the right field ($+127^\circ$ via 180° to -139°) and the left monkeys the left field ($+90^\circ$ via 0° to -131°).

In general, therefore, we get the impression that, at least preponderatingly, *the electrical axis of the S-T deviation tends to point in the direction of the distribution of the ligated artery; in the direction, that is to say, of the developing heart lesion.*

If the monkey lives long enough, in our experience at least two days, this developing heart lesion will, as a rule, manifest itself later morphologically although in all probability never in its original size, since, depending on the possibilities of collateral circulation, some repair will take place at the periphery, as described in other animals.^{32, 34} It is probable that these possibilities will be greater in animals that were originally healthy than, for instance, in patients with pathologically altered heart vessels.^{35, 36}

TABLE IV A

SITE OF LESIONS FOUND MICROSCOPICALLY IN LEFT MONKEYS

MONKEY	SURVIVAL AFTER OPERATION	SITE OF LESION*
4 L	6 mo.	Anterolateral part of L. V., middle and apex. Also septum lesion.†
6 L	7 wk.	Anterolateral part of L. V., middle and apex; at apex crossing over to R. V. Also septum.
9 L	5½ mo.	Lateral part of L. V., middle and apex. Also septum.
17 L	2 days	Anterolateral part of L. V., middle and apex. No septum lesion.
19 L	2 mo.	Beginning midway in sulcus interventr. ant., enlarging in apical direction, at apex occupying whole ant. and lat. part of L. V., and ant. part of R. V. Also septum.
44 L	1½ mo.	Anterolateral part of L. V., only at middle, not reaching base or apex. No septum lesion.
49 L	5 days	Anterolateral part of L. V., principally at middle, less at apex. No septum lesion.
51 L	1 mo.	Exclusively at apex, occupying anterolateral part of L. V. and whole apical part of R. V. Also septum lesion.
53 L	1 mo.	Anterolateral part of L. V., principally at middle, a little at apex, not at base. Also septum lesion.

*L. V. = left ventricular wall; R. V. = right ventricular wall.

†Septum lesions described later. See also Fig. 11.

Lesions were found in the monkeys shown in Tables IV A and IV B. In all these animals, as well as in the others described, the microscope confirmed the efficiency of the ligation.*

We shall discuss further the site of these lesions† in Part III of this paper.

*The microscopie examination of the hearts and also the larger part of the autopsies were carried out under the personal supervision and control of Dr. H. Müller, Director of the Pathological Institute of the Medical School at Soerabaja, and during the operative part of our researches acting-director of the Pathological Institute at Batavia, and with the cooperation of our student assistant, J. H. Jansen. It is a pleasure to express our thanks for their valuable assistance.

†The microscopie details of the lesions will not be discussed. The position and extent of the lesions were confirmed by Dr. H. Müller, and their boundaries were drawn under his supervision by J. H. Jansen, as they showed in heart sections in 7 equidistant planes, lying perpendicularly to the heart axis, beginning at the base, ending at the apex.

The following method was used for the microscopic examinations: Fixation of the heart in 5 per cent formalin; organ cut into slices of about 1 cm. perpendicularly to axis and embedded in eedocol; sections made of 30 microns. At least each tenth section was studied microscopically, being finally stained with eosin and hematoxylin.

TABLE IV B

SITE OF LESIONS FOUND MICROSCOPICALLY IN RIGHT MONKEYS

MONKEY	SURVIVAL AFTER OPERATION	SITE OF LESION*
10 R	6 mo.	Wall of R. V., at base larger than at apex, extending to posterior side and post. part of septum.† At apex also extending to posterior part of L. V.
11 R	6 mo.	As 10 R, only not extending to posterior apical part of L. V. Also septum lesion.
12 R	5½ mo.	Lateral wall of R. V. except the apex. No septum lesion.
14 R	4 mo.	Middle anterior third of R. V., not reaching base or apex. No septum lesion.
31 R	1 mo.	Exclusively small anterior part of R. V. near conus arteriosus. No septum lesion.
41 R	4 days	Anterior, lateral, and posterior part of R. V., especially at middle and at base. Also septum lesion.
43 R	1½ mo.	Exclusively lateral part of R. V., principally at the base, not reaching the apex. No septum lesion.
56 R	3 wk.	Lateral middle part of R. V., not reaching base or apex. No septum lesion.

*L. V. = left ventricular wall; R. V. = right ventricular wall.

†Septum lesions described later. See also Fig. 11.

We have measured the direction of the S-T deviation in the way described above, as far as possible, at that time after the operation at which it had reached its maximum development.

If the measurements were made at other times, it appeared that the manifest magnitude was different but that the direction of the electrical axis varied very little, in our experience as a rule not more than about 20°, often less. This is a variation which approaches in magnitude the possible errors in measurement. Another factor may perhaps be the influence of the respiratory phases since it is impracticable to make all measurements in one given respiratory phase.

Figure 5 gives an example of an S-T axis which kept its direction of +90° for thirty-three days. The rather small oscillations, which were observed in those cases where the S-T deviation existed longest, are given in Table V.

TABLE V

SEE TEXT

MONKEY	DIRECTION OF ST AXIS		DIFFERENCE	
	IN MAXIMAL DEVELOPMENT	LATER	IN DIRECTION	IN TIME
9 L	+ 60°	+ 35°	25°	5 mo.
19 L	+ 99°	+ 90°	9°	2 wk.
44 L	- 49°	- 47°	2°	1 mo.
51 L	+ 90°	+ 90°	0°	1 mo.
53 L	- 60°	- 79°	19°	1 mo.
10 R	+117°	+150°	33°	3 mo.
43 R	+150°	+150°	0°	12 days
56 R	+ 90°	+ 90°	0°	1 wk.

We shall discuss later Monkey 4 L (A and B) which seems to be an exception to this rule.

Monkey 6 after the left ligation (6 L) showed a mixed type ($+127^\circ$), but after the second operation seven weeks later, when a right ligation was also done, it showed a right type (-160°). In this case (6 L + R), therefore, it is probable that the artery last ligated or the latest lesion to develop impressed its influence on the electrocardiogram (Part II, Fig. 12).

Monkey 23 R showed for a short time an S-T direction of $+160^\circ$ (type A), afterward of $+150^\circ$ (type B), the S-T segment again becoming isoelectric in Lead II (Part II, Fig. 15).

In regard to the *secondary changes in the ventricular electrocardiogram*, which arise later, we must state that in practically all the monkeys

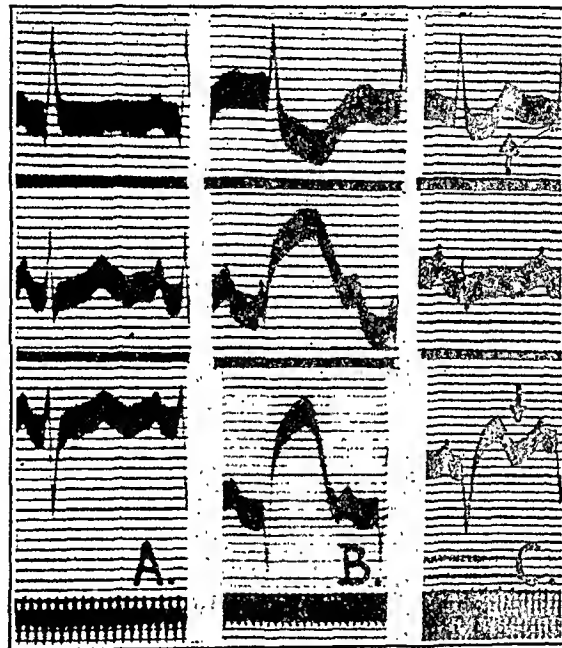


Fig. 7.—Monkey 10 R. A, before operation; B, 63 min., and C, 3 weeks after ligation of right coronary artery. See also Part II, Figs. 3, 4, 5, and 10.

(with the exception of those in which fibrillation rapidly ensued) we observed to a greater or less degree the phenomenon first described by Parkinson and Bedford,³⁵ namely the development of an after-wave during the reduction of the S-T deviation and developing in the opposite direction.

Examples of this are shown in Fig. 7 (segment C) and several other of our illustrations (Figs. 5E, 8C, 9D, 10D, 12C, and 16D).

The last mentioned authors have shown that this secondary after-wave developed in such a way that its apex just coincided with the end of the previously existing ventricular complex, in other words that the development of this secondary wave was accompanied by a prolongation of the (electrical) systole. Our curves confirmed this statement.

If now for the sake of brevity we call the electrocardiogram obtained immediately after the ligation (in which as a rule the S-T deviation is already present, but the secondary after-wave still absent) the primary coronary electrocardiogram (prim.) and the curve in which the after-wave has developed the secondary coronary electrocardiogram (sec.), it must be noted that the former seldom shows any prolongation or shortening of the ventricular systole in comparison with the original electrocardiogram (orig.), while the latter almost without exception shows a prolongation, even when account is taken of possible changes in the heart rate.

Examples of this are given in Table VI.

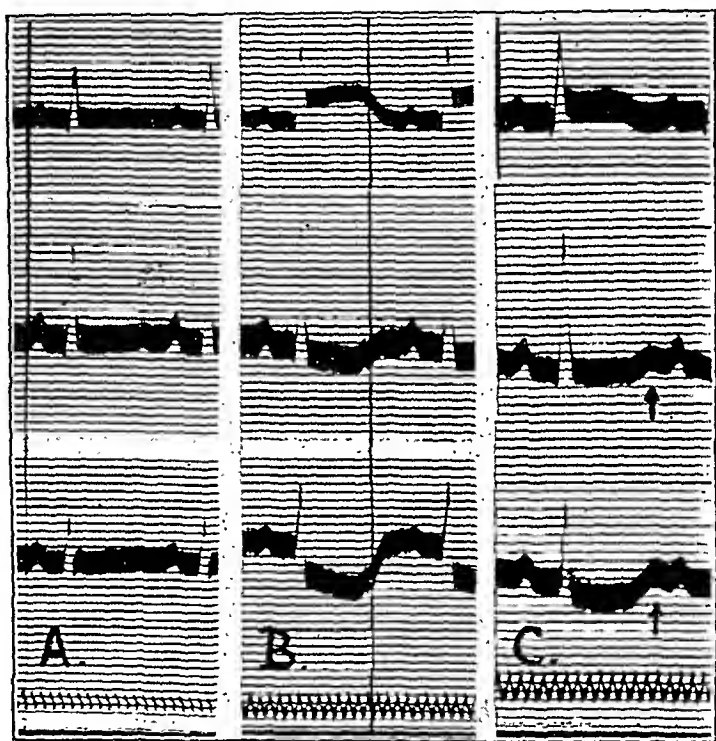


Fig. 8.—Monkey 49 L. A, before operation; B, 63 min., and C, 3½ hours after ligation of the ramus descendens anterior.

In Part III of this paper we shall consider again the subject of this time relationship.

It must still be pointed out that in making these time measurements attention must be paid to the lead in which they are most clearly to be seen. It can even happen after ligation that in one lead the ventricular complex more or less retains not only its length but also its form, whereas in the other leads both prove to be considerably altered. An example of this is shown in Part II (Fig. 15 there), in which in the secondary coronary electrocardiogram of Monkey 23 R the ventricular complex lasted 0.26 second in Leads I and III, and at the same time 0.23 second in Lead II. The final swings in Leads I and III so nearly compensated one another that in Lead II the string returned to the diastolic line earlier than in the other leads. Lead II, except for the fact that a nodal rhythm developed, had the same form as far as the ventricular complex is concerned as before the operation, while in Leads I and III this complex markedly changed.

QRS Changes.—In addition to the electrocardiographic changes described above, *changes in the QRS complex* were observed in several of the monkeys.

In a detailed study of this complex and the attributing of definite value or significance to changes observed in it, the question must always be asked whether in any given instance technical or instrumental errors are playing a part (a still greater liability in recording the very rapid electrical variations of the monkey heart), or whether either displacements of the heart or differences in the respiratory phases may be responsible.

TABLE VI

Examples showing prolongation of ventricular complex in secondary coronary electrocardiogram (sec.) and absence thereof in primary coronary electrocardiogram (prim.) in comparison with the original electrocardiogram (orig.).

MONKEY	TYPE ECG	LENGTH VENTR. COMPL.	HEART RATE	MONKEY	TYPE ECG	LENGTH VENTR. COMPL.	HEART RATE
4 L	orig.	0.15	236	51 L	orig.	0.17	240
	prim.	0.15	236		prim.	0.17	222
	sec.	0.21	214		sec.	0.19	231
5 L	orig.	0.15	260	10 R	orig.	0.18	196
	prim.	0.16	245		prim.	0.18	200
17 L	orig.	0.22	158		sec.	0.21	191
	prim.	0.24	143	11 R	orig.	0.17	214
	sec.	0.26	143		sec.	0.21	194
35 L	orig.	0.18	240	36 R	orig.	0.19	188
	prim.	0.19	192		prim.	0.18	188
	sec.	0.20	201	43 R	orig.	0.22	188
44 L	orig.	0.19	204		prim.	0.22	176
	prim.	0.19	204	56 R	orig.	0.16	206
	sec.	0.19	195		prim.	0.16	206
49 L	orig.	0.18	214		sec.	0.17	214
	prim.	0.18	203				
	sec.	0.21	210				

Particular attention was paid to these considerations.

In our opinion the following QRS changes (Table VII) may be regarded as resulting from the interruption of the coronary circulation and the internal changes in the heart caused thereby. Since a possible connection with septum lesions appeared, the findings in that direction are also given (see also Fig. 11).

These observations are summarized in Table VIII.

We regard these observations as too small in number to allow us to draw conclusions from them with certainty as to differences between the results of left and right ligation.

Some connection between QRS changes and S-T displacement might be deduced from the fact that in all cases in which there was an increase in the Q-wave in any given lead, S-T ascended in the same lead (see also Wilson and his associates³³ and Parkinson and Bedford³⁵ and Fig. 9), while in all cases in which the Q-wave was reduced the corresponding S-T descended.

However, there is no direct parallel, since the QRS changes are not always maximal at the time when the S-T displacement is maximal, but

often later, during the recession of the deviation and the development of the secondary after-wave (see, for instance, Fig. 5). Moreover, the S-T deviation and after-wave could develop without there being any QRS change (see Figs. 10 and 16), but, on the other hand, we never saw a change in the QRS complex in a monkey which did not also show a displacement of the S-T segment. For this reason we are not justified in considering the prolongation of systole, which is practically always observed during the existence of the QRS change, as having a relationship especially or only to this latter change.

TABLE VII
DATA CONCERNING QRS CHANGES

MONKEY	INCREASED OR DEVELOPED	DECREASED OR DISAPPEARED	FIRST SEEN AFTER OPERATION	DURATION OF LIFE AFTER OPERATION	SEPTUM LESIONS FOUND*
4 L	Q ₁	-	5 mo. (4 B)	6 mo.	yes
6 L	Q ₂ , Q ₃	-	7 wk.	7 wk.	yes
9 L	Q ₁ , Q ₂	-	35 min.	5½ mo.	yes
16 L	Bundle-branch block	-	5 min.	13 min.	no
19 L	S ₁ , S ₂	-	45 days	2 mo.	yes
51 L	Q ₂ , Q ₃	-	33 min.	1 mo.	yes
53 L	S ₁ , S ₂	-	20 days	1 mo.	yes
6 L+R (after R lig.)	S ₁ , S ₂	Q ₂ , Q ₃	10 min.	7 wk. after L. 2 hr. after R.	yes (probably from L.)
10 R	-	Q ₁	57 min.	6 mo.	yes
11 R	Q ₁ ?	Q ₂	3½ mo.	6 mo.	yes
36 R	S ₁	Q ₂	52 min.	6 hr.	no
37 R	S ₁ , S ₂	Q ₁ , Q ₂	17 min.	1 hr.	no
41 R	S ₁ , S ₂ Q ₂ , Q ₃	Q ₁ , Q ₂ S ₁ , S ₂	26 min. 1 day	4 days	yes

*See also Fig. 11.

TABLE VIII
SUMMARY OF THE RESULTS TABULATED IN TABLE VII*

TOTAL NUMBER OF MONKEYS IN WHICH:												
	Q ₁		Q ₂		Q ₃		S ₁		S ₂		S ₃	
	+	-	+	-	+	-	+	-	+	-	+	-
After L. ligation	2	0	3	0	2	0	0	0	2	0	2	0
After R. ligation	0 (1?)	3	1	5	1	1	3	1	4	1	0	0

*+ = development or increase.
- = disappearance or decrease.

At this time we must be satisfied with saying that undoubtedly the most important prolongations appeared to be connected with the presence of the after-wave and not with that of the QRS changes. If the latter appeared before the after-wave then in one case (Monkey 36 R), with the heart rate unchanged, the systole even appeared to be shortened, whereas whenever there was an after-wave without any change in the QRS complex, systole was prolonged.

Summarizing, we may say that S-T deviations were repeatedly seen without changes in the QRS complex, at least in that part of it which

remained visible; that QRS changes were never observed without S-T deviations, although as a rule they became apparent only when the S-T changes were decreasing, and that no definite connection between a QRS change in itself and an altered duration of systole could be observed.

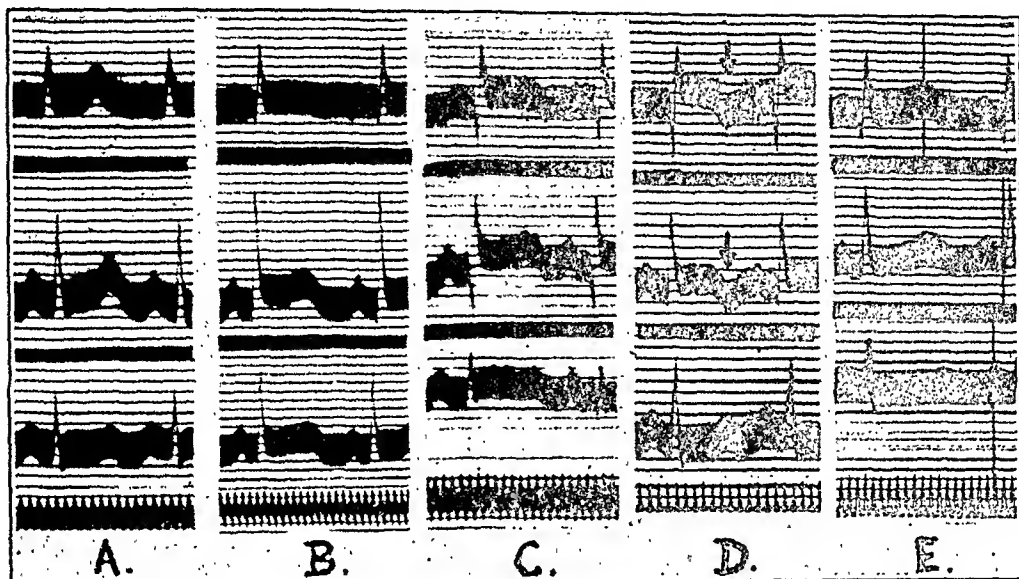


Fig. 9.—Monkey 9 L. A, before operation; B, 35 min., C, 1 day, D, 34 days. E, 5½ months after ligation of the ramus descendens anterior. Example of S-T deviation with changes in QRS.

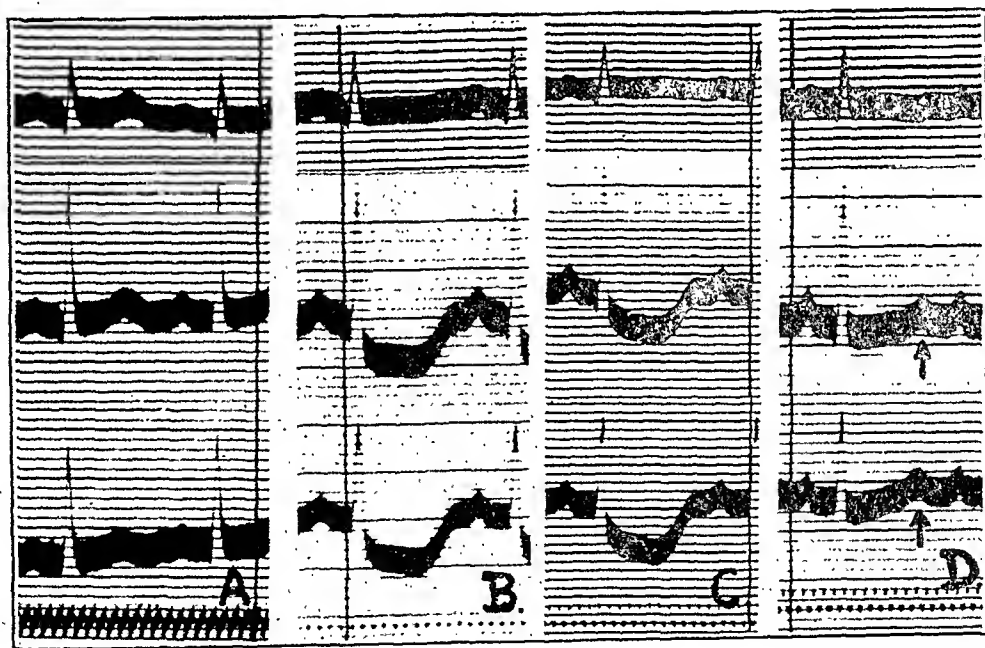


Fig. 10.—Monkey 35 L. A, before operation; B, 13 min., C, 88 min., D, 6 hours after ligation of the ramus descendens anterior. Example of ST deviation without changes in QRS.

Although as a rule the course of development of a possible QRS change proved to be slower than that of the coexistent S-T deviation, we could not determine with certainty from our curve material which of the two disturbances remained longer in evidence. We never observed late QRS changes unaccompanied by other changes, as Wilson

and his associates³³ did in man. There was in our monkeys always a residual S-T deviation or after-wave still showing.

In the literature QRS changes are often connected with function disturbances of the intraventricular conduction system, especially in the septum.³⁷⁻⁴⁰ We requested the pathologist, therefore, to pay attention particularly to the septum. In Table VII we have already stated in which of our animals showing QRS changes septum lesions were found. That they were not visible in Monkeys 16 L, 36 R, and 37 R (also 6 L + R especially after right ligation) may be due to the fact that these animals survived the operation only so short a time. There may well have been functional disturbances in the septum in these cases.

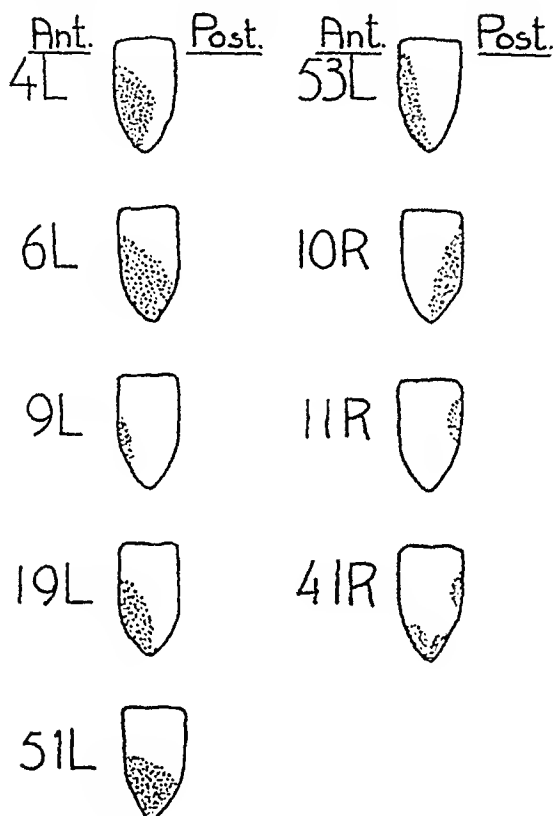


Fig. 11.—Showing location of septum lesions found in the monkeys.

Figure 11 shows in which monkeys septum lesions were found and where they were located.

In general these lesions were more severe in the left monkeys than in those in which right ligation had been performed, which coincides with what might be expected from the description of the circulation relations in the septum given before. After left ligation the lesions were principally below and anterior; after right ligation, if present at all, principally in the middle portion posterior and of comparatively small size.

If we combine the results shown in Fig. 11 with the data of Table VII, we come to the following conclusions.

In thirteen monkeys QRS changes were present. In nine of these also septum lesions were found microscopically. In the remaining four (including Monkey 6 L + R after right ligation) no such morphologically visible lesions were to be expected because these monkeys survived too short a time. In all other monkeys used in these experiments, neither QRS changes nor morphologically visible septum lesions were present, although there were among them seven animals which survived the operation considerably longer than two days (the minimum interval after the ligation, in which lesions became recognizable).

Therefore, we regard it as very probable that there is a connection between QRS changes and function disturbances of the septum, at least in monkeys.

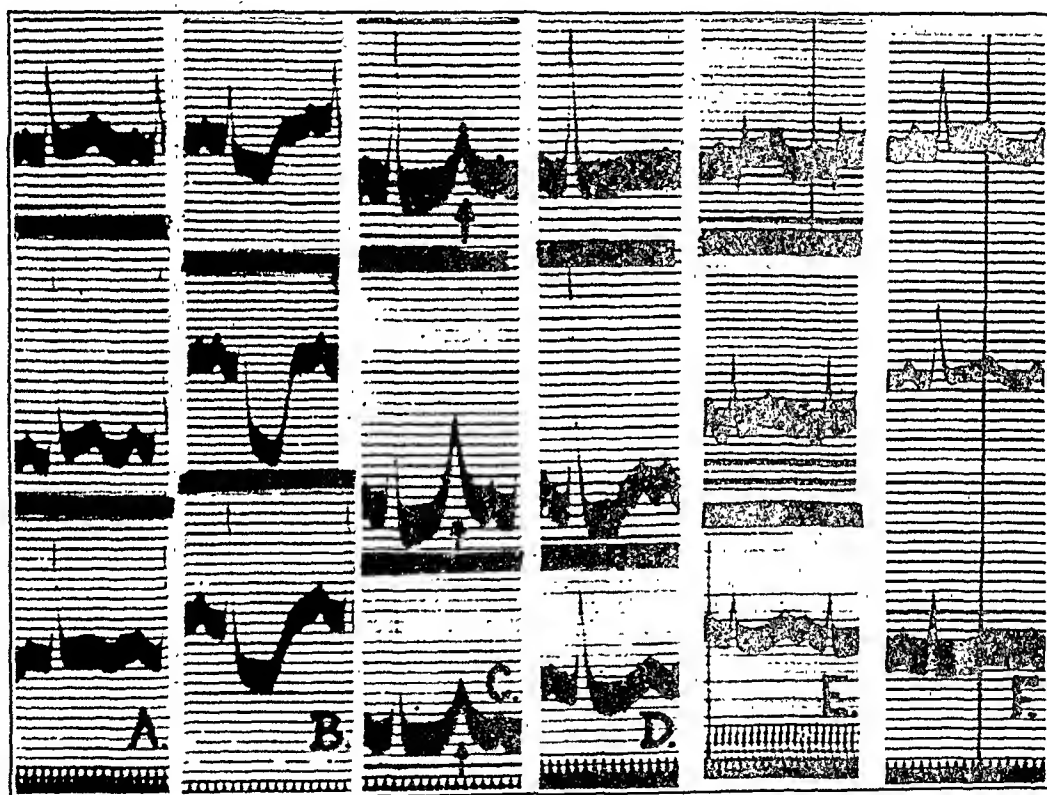


Fig. 12.—Monkey 4 L. A, before operation; B, 50 min., C, 1 day, D, 8 days, E, 5½ months, F, 6 months after ligation of ramus descendens anterior. B is described in text as type A, E as type B of this monkey.

Let us now consider on the basis of the following extracts from our work to what extent the animals which survived the operation longest again showed their original electrocardiogram. In other words, what were the last remaining traces of the changes in the ventricular complex?

It may be noted beforehand that our observations show that in general an electrocardiogram which after ligation had once become altered never quite returned to normal. Changes remained both in the configuration and in the time relationships. In this connection, however, it should be pointed out that none of our animals was allowed to survive the operation longer than six months.

Monkey 4 L.—After six months the S-T segment in Leads I and II was too high, in Lead III slightly too low. The length of systole had risen from 0.15 to 0.20 sec., the heart rate had fallen only from 236 to 208. The peculiarity of this animal was the development of a second type of S-T deviation, observed about five months after the operation. It seems possible that the first deviation (4 A: -117°), observed directly after the operation, is connected with the septum lesions found in this monkey; the second deviation (4 B: $+5^\circ$) with the heart aneurysm that proved to be present in the so-called anterior wall of the left ventricle about one-third of the length of the ventricle from the apex, adjoining the septum. It should, however, be noted that the QRS change (Q_1) was observed only in Type 4 B (see Figs. 12 and 13).

Monkey 9 L.—As shown in Fig. 9 the S-T segment was still too high, especially in Leads I and II, five and one-half months after the operation. Of interest was the development of Q_1 and Q_2 , of which Q_1 appeared first and remained the longer. Be-

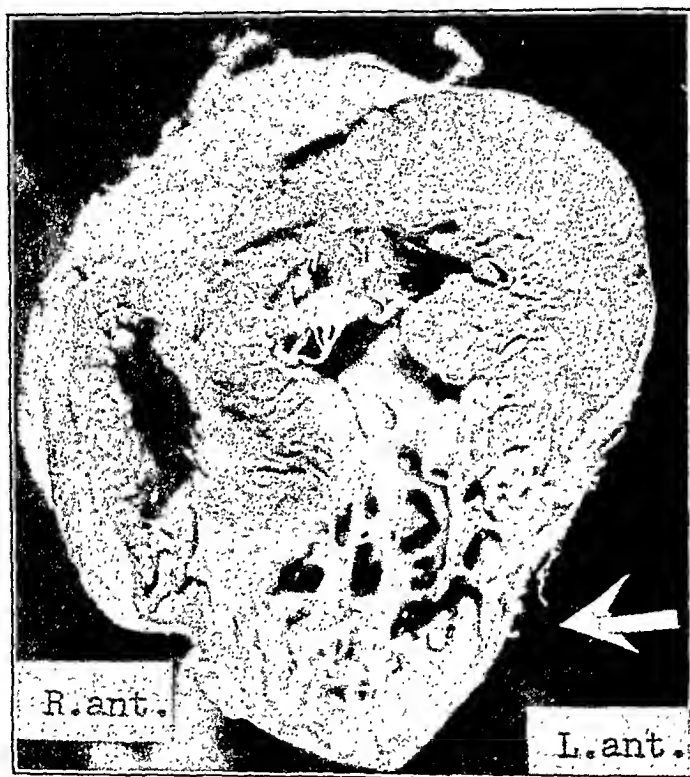


Fig. 13.—Monkey 4 L. Aneurysm of left ventricular wall, involving anterior part of septum, 6 months after ligation of the ramus descendens anterior.

tween the first and last curve there was, besides the Q_1 and the S-T deviation, this further difference that in the latter, in spite of a reduced pulse rate, the systole must be regarded as relatively prolonged (first curve 0.15 sec., with a frequency of 220, final curve 0.20 sec. with a frequency of 166).

Monkey 19 L after two months still showed traces of the after-wave, as well as a definite S_2 , which was previously not present, and an increased S_2 . The systole appeared to be prolonged in the final curve which, however, showed too many incidental vibrations for accurate measurement.

Monkey 10 R after five months still showed traces of the original S-T deviation, as well as a definite after-wave and a prolonged systole at a higher heart rate (originally 0.18 sec. with a frequency of 196, finally 0.20 sec. with a frequency of 218). Furthermore there were changes in the QRS complex, Q_1 was still absent. (See for this monkey Fig. 7 and in Part II, Figs. 3, 4, 5, and 10.)

Monkey 11 R.—After five months the electrocardiogram at first sight closely resembles the original. The T-wave is, however, somewhat changed in form, the isoelectric part between R and T is prolonged and in Lead III is convex and followed by a negative T_2 , remains of the after-wave perhaps. The systole is relatively shortened, the pulse less frequent (originally 0.17 sec. and 214, final curve 0.17 and 171). Q_1 seems still slightly increased.

Monkey 12 R.—There appeared after five months in Leads I and II a high sharp positive T-wave following a negative S-T segment in both leads and a negative T_2 following a positive S-T segment in Lead III. The length of systole was shortened from 0.19 to 0.15 sec., the pulse rate, however, had risen from 204 to 252. (See for this monkey Fig. 14, and Part II, Fig. 6.)

Monkey 14 R.—The final curve taken after four months showed too many incidental vibrations for detailed study. In general the electrocardiogram of this

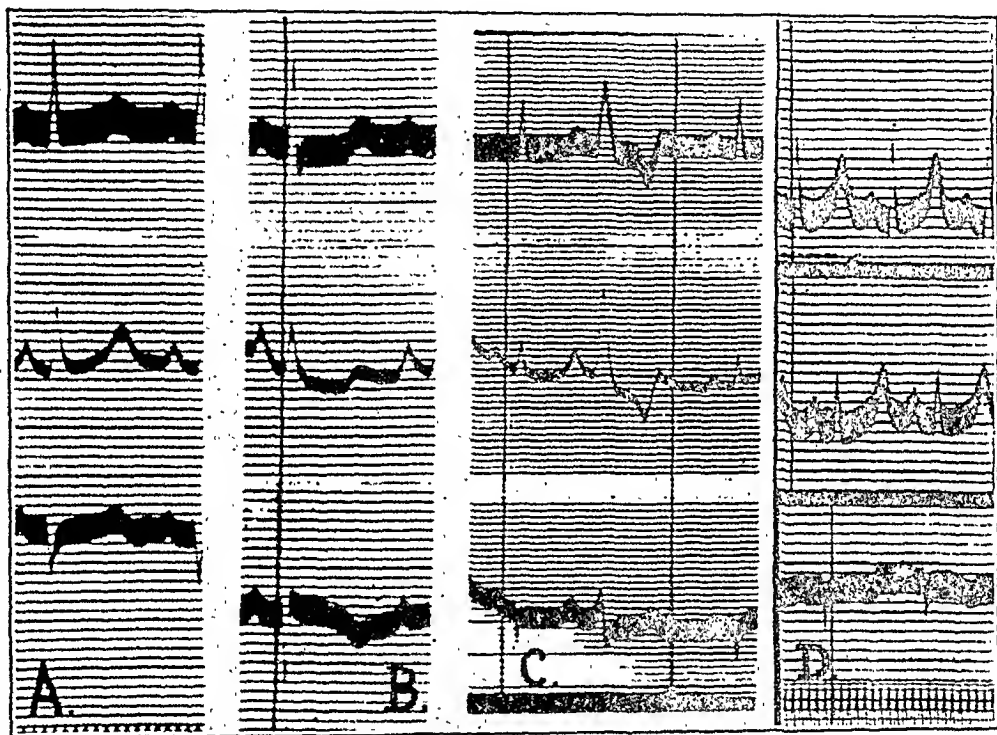


Fig. 14.—Monkey 12 R. A, before operation; B, 85 min., C, 1 day, and D, 5 months after ligation of right artery. In C extrasystole from right ventricle, apical part, interfering with P-wave. See also Part II, Fig. 6.

animal appeared not to be noticeably altered during the entire course of the observations, a fact which we ascribe to the frontal position of the lesion, as will be explained in Part III of this paper.

Monkey 31 R.—After about one month there was a markedly negative T_1 and positive T_2 . There had been formerly no definite S-T deviation. The visible lesion was, as in 14 R, situated well to the front (see also Part III). It was limited to the conus arteriosus, in all probability because only the corresponding small branch of the right artery had been ligated. Apparently an after-wave had developed without any clear ST deviation preceding. Systole was definitely prolonged (originally 0.18 sec. and pulse rate 194, finally 0.21 sec. and 206).

Monkey 43 R (see Fig. 15).—After one and one-half months the electrocardiogram shows similarities with the original curve, although the T_2 , perhaps not unconnected with the small negative after-wave formerly developed in III (Fig. 15 C), is not yet positive. In view of the fact that P begins before the end of T no measurements of the length of systole are possible.

Monkey 56 R (see Fig. 16).—After three weeks the S-T deviation had disappeared, but there was still a clearly observable after-wave present especially in Leads II and III. Systole was prolonged (originally 0.16 sec. and pulse rate 206, finally 0.17 sec. and 214).

Before passing on to Part II of this paper, we shall discuss briefly two special cases in which the electrocardiogram reminded us of that found after ligation.

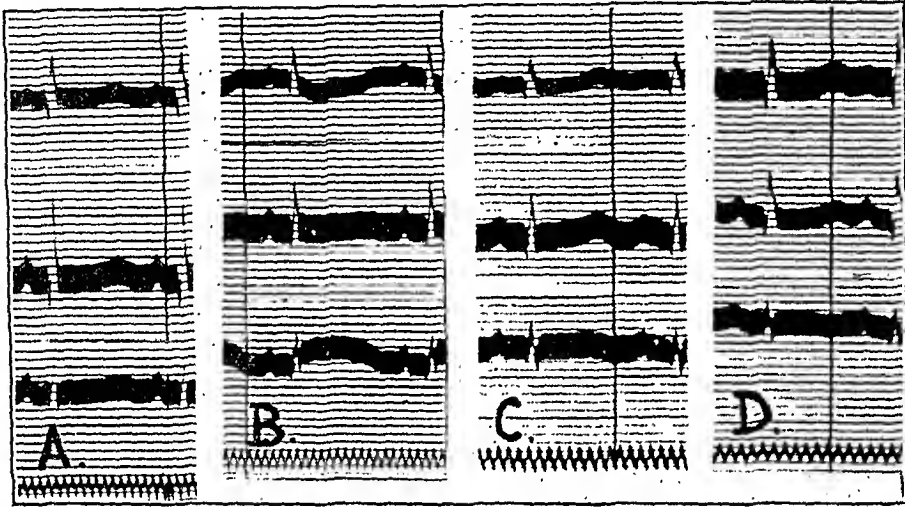


Fig. 15.—Monkey 43 R. A, before operation; B, 75 min., C, 9 days, D, 1½ months after ligation of right artery.

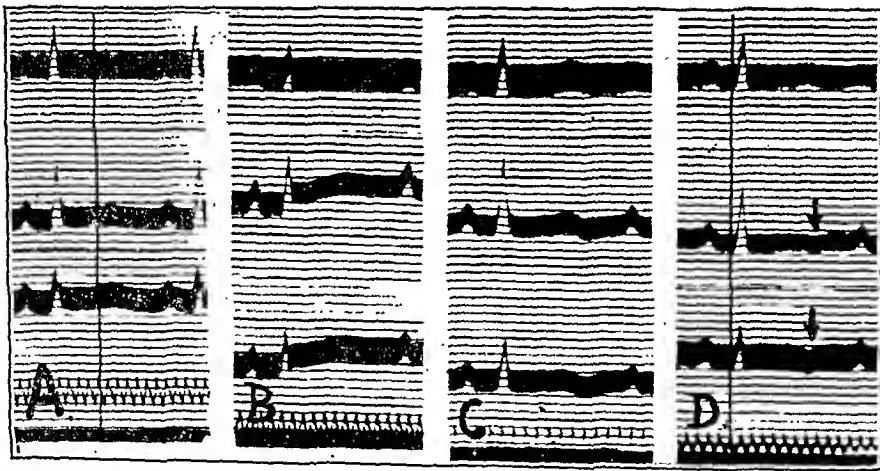


Fig. 16.—Monkey 56 R. A, before operation; B, 2 hours, C, 2 weeks, and D, 3 weeks after ligation of right artery.

1. It has been mentioned⁴¹ that death following *air embolism* might in many cases be due to the closing off of one or more of the coronary arteries or some of their branches, and in such instances electrocardiograms were obtained closely resembling the “coronary type.”

We injected into the femoral vein of Monkey 16 B several cubic centimeters of air. Within a couple of minutes (see Fig. 17) there appeared a deviation of the S-T segment. There was a temporary nodal rhythm with extrasystoles originating in

the right apex. The heart later returned to a slowed sinus rhythm with an increase of the S-T deviation. Finally, after fifteen minutes, ventricular fibrillation was visible in the string movements. The S-T axis pointing at an angle of $+106^\circ$ (mixed field) gave no definite evidence in favor of left or right obstruction. The apparently localizing extrasystoles might have been due to an increased resistance in the

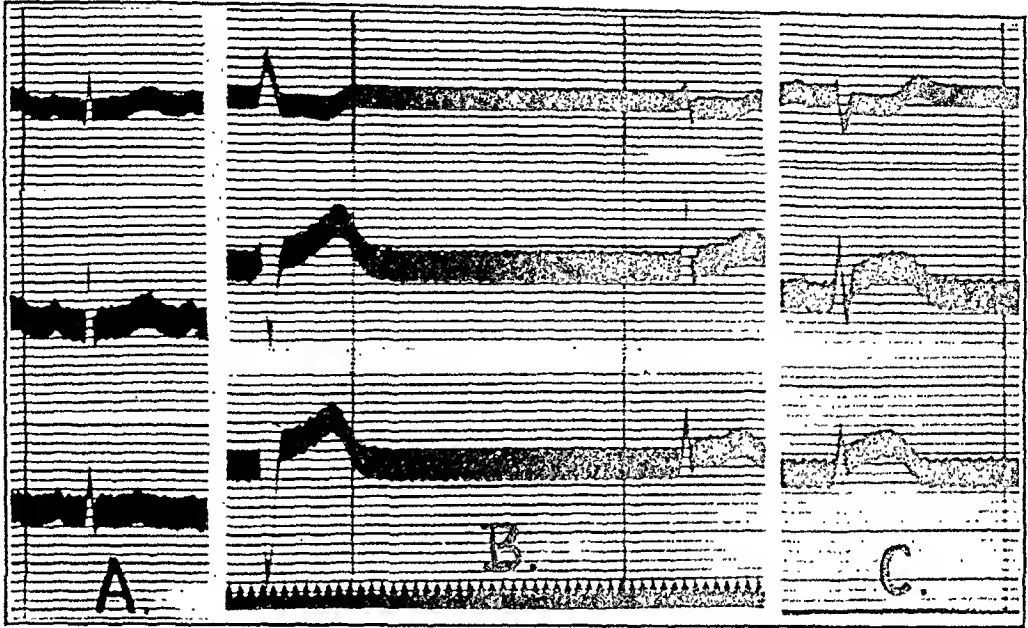


Fig. 17.—Monkey 16 B. A, before experiment; B, 5 min., C, 10 min. after injection of air into vena femoralis. In B, note extrasystole of right apex type and nodal rhythm.

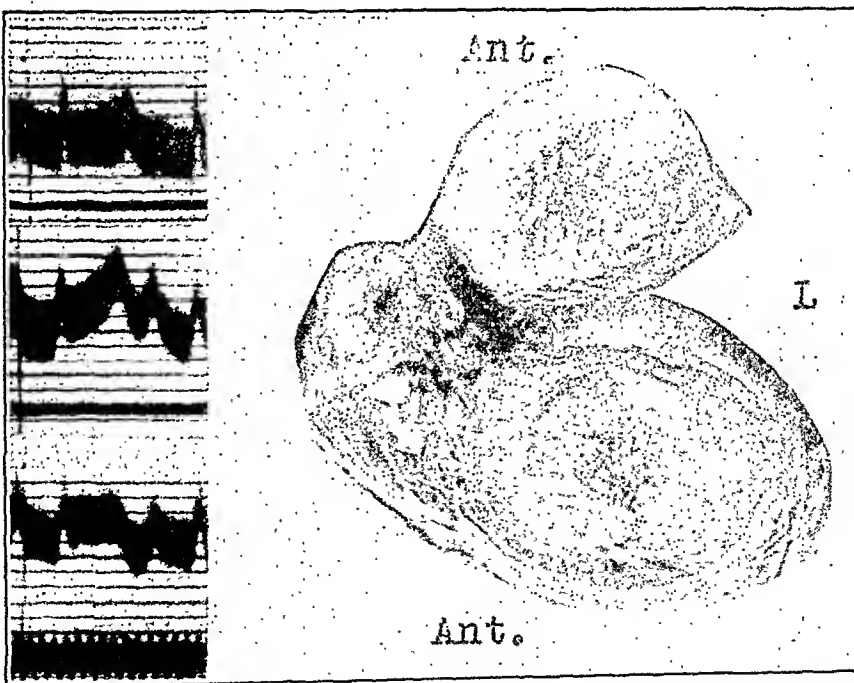


Fig. 18.—Monkey 27. Electrocardiogram before operation showing S-T deviation in Leads II and III, and heart showing spontaneous disease, visible as white patches in musculature.

pulmonary circulation, in which case probably both coronary arteries would get too little blood. Dr. Müller performed the autopsy and found the right heart filled with air. Undoubtedly there had been a disturbance of the coronary circulation due to some cause operating within the cardiovascular system. The rapid appearance and subsequent disappearance of the nodal rhythm also points in this direction.

It seems useful to report this case since it supports our opinion that similar electrocardiographic changes obtained by ligation of the arteries are not dependent on damage to nerves that accompany the arteries. As a matter of fact, others¹⁹ have obtained similar changes in the electrocardiogram in dogs when the occlusion of the arteries had been produced from within with lycopodium. With the single exception of air embolism, described above, we were not able to use successfully in our monkeys methods by which the arteries are obstructed from within, although in some animals efforts were made to pass sounds from the carotid into the coronary orifices.

2. The second special case concerned a *pathological monkey heart*.

In all our healthy monkeys we found the S-T segment constantly isoelectric. When, therefore, in Monkey 27, as an exception, even before operation, the curve reproduced in Fig. 18 was found, in which the S-T segment in Leads II and III was abnormally high (S-T direction $+90^\circ$), the operation was not performed and the animal was immediately killed for investigation.

The following report was received from Dr. H. Müller: "In addition to changes in the liver and spleen, white patches were clearly visible even macroscopically in the heart muscle at the apex of the left and right ventricles. Microscopically there were peculiar changes in the muscle fibers in these regions, which were swollen by large vacuoles. There were signs of muscle degeneration and a few indications of regeneration. A toxic infectious origin seems probable."

SUMMARY

Reasons are given why monkeys offer many advantages over other animals for experimental heart research, especially for electrocardiographic research, in spite of the fact that the anatomical structure of their coronary system sometimes differs from that of man. This anatomical structure and its relationship to that of man are described in the Javanese monkey *Macaca irus*. After the normal electrocardiogram and the influence of various incidental factors on it had been studied, coronary vessels were ligated in these monkeys. In seventeen of the animals described, the anterior descending branch of the left artery (L) was tied off and in fourteen the right artery (R). In one monkey the right artery was ligated seven weeks after the anterior descending branch of the left. The electrocardiograms were recorded in the customary Leads I, II, and III, mostly simultaneously. S-T deviations were shown by all monkeys, except two left monkeys which fell immediately into ventricular fibrillation, and two right monkeys which afterward were shown to have exclusively frontal lesions. The S-T deviation appeared within ten minutes, reached its maximum in about one hour, and disappeared in an average time of one month. The S-T deviation must always be observable in at least two leads; its study in only one lead is of but little value. The direction of the S-T deviation

(the electrical S-T axis) was determined, according to the principles of the equilateral triangle, by quantitative measurements in at least two leads. This direction proved to point after left ligation preponderatingly to the left, and after right ligation preponderatingly to the right. There was a small mixed sector, in which the S-T axes of left and right monkeys were shown to overlap. During development of the S-T deviation systole is usually not prolonged. Among the secondary changes in the ventricular electrocardiogram there was often observed an after-wave in a direction opposite to that of the preceding S-T deviation. This was accompanied by a prolongation of systole. Changes in the QRS complex are described in thirteen animals. No definite direct relation between those changes and an altered duration of systole could be found. There appeared to be a probable connection between those changes and septum lesions. An electrocardiogram that after ligation had once changed never returned within six months to its original form completely. Two special cases (one of air embolism and one of a spontaneous heart disease) are described, in which in the monkeys concerned the electrocardiogram resembled that after coronary ligation.

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THE USE OF INTERMITTENT VENOUS COMPRESSION IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE*

A PRELIMINARY REPORT

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THE inadequacy of present methods in the treatment of peripheral vascular disease is exemplified by the large number and variety of methods employed. It simply speaks for the insufficiency of any one method. The various measures used to date have consisted of the following: (1) bed rest;¹ (2) physiotherapy consisting of the application of heat by baking, baths, and diathermy;²⁻⁴ (3) postural exercises;⁵ (4) elimination of all spasm-producing substances such as: (a) tobacco,^{6, 7} (b) exposure to cold, (c) ergot-containing foods such as rye bread and pumpernickel;⁸ (5) the use of vasodilating drugs such as: (a) theobromine,⁹ (b) acetyl-beta-methylcholine,¹⁰ (c) alcoholic beverages,¹¹ (d) hot drinks,¹² (e) papaverine,¹³ (f) calcium,¹⁴ (g) parathyroid hormone;¹⁵ (6) reflex vasodilatation produced by immersion of upper extremities in hot water, such as employed in the Landis test;¹⁶ (7) operative procedures for the production of vasodilatation, such as ganglionectomy or arterial stripping of Leriche;^{17, 18} (8) intravenous injections of hypertonic solutions of either sodium chloride or buffered sodium citrate;^{19, 20} (9) intravenous typhoid vaccine and other foreign proteins;²¹ (10) alcohol injection of peripheral nerves;²² (11) pancreatic extract (insulin-free);²³ (12) mechanical methods of improving circulation by alternate suction and pressure;²⁴ (13) femoral vein ligation.²⁵⁻³² A critical survey of the efficacy of the above methods is outside the scope of this paper.

An interesting series of experiments³³ dating back to the latter part of the nineteenth century has led to a physiological observation which hypothetically should possess a practical application to the treatment of peripheral vascular disease. We refer to the phenomenon of "reactive hyperemia." By reactive hyperemia is meant a flush or hyperemia which develops during the release of obstruction to circulation of an extremity. It has been demonstrated that this phenomenon is totally independent of nerve innervation.

In a very comprehensive study on the reaction to venous obstruction, Lewis and Grant³⁴ made the following observations: 1. If a pneumatic cuff be applied to an extremity and pumped up to 25 mm. of mercury pressure, an increase in the volume of the extremity, as recognized by means of plethysmographic methods, occurs within fifteen seconds. 2.

*From the Metabolic Clinic of the Israel Zion Hospital.

The degree of increase in volume is directly proportional to the increase in pressure up to 90 mm. of mercury. 3. At the end of fifteen minutes of compression, a definite increase in volume pulse occurs. 4. With the release of pressure, there is first a fall, then a rise in volume. The greater the original pressure, the greater is the secondary rise. 5. Heating the extremity accentuates the amplitude of this phenomenon. 6. This secondary rise, called a "hump," indicates that simple venous congestion may produce a vasodilatation similar to that which occurs when an occluded artery is released. 7. They believe that the release of venous congestion is associated with both active and passive vasodilatation of the arterioles. 8. The most important observations which these authors make, from the standpoint of our studies, is that there occurs, *during the release* of venous congestion, an increase in arterial flow of as much as 600 per cent, depending upon the degree and duration of applied venous congestion.

It would appear, then, that obstruction to venous flow is associated, when this obstruction is released, with an active vasodilatation of the arteries and a remarkable increase in arterial flow.

A large series of studies, both in the experimental animal and in the human, have been carried on in the past with the view of stimulating arterial flow through diseased vessels by obstructing the venous return.²⁵⁻³² The experimental procedure²⁵ has consisted of the simultaneous ligation of the femoral vein and artery without the eventual production of gangrene. This observation in the dog led to subsequent femoral vein ligations in humans suffering from either thrombo-angiitis obliterans or peripheral vascular sclerosis. Some workers have felt that there is a measure of value in this procedure,³¹ while others have been more skeptical.³⁰

On the basis of the careful studies of Lewis and Grant, it appears that the benefit to be derived from venous obstruction comes, not as a result of the obstruction per se, but from the *release* of an obstruction. It is on this basis that we feel there is a fallacy in the ligation of the femoral vein for the treatment of peripheral vascular disease.

We have attempted to alter this procedure sufficiently to incorporate the beneficial effects of venous obstruction and release by utilizing an apparatus (described in the following paper) designed to produce alternating periods of venous congestion and release of congestion.

After a preliminary trial of the application of various degrees and lengths of time of venous compression, we arrived at what appeared to be an optimal technic. We found it impracticable to apply the higher pressures which Lewis and Grant observed to produce maximal increases in circulatory flow in normal, because these levels produced considerable pain in extremities with occluded vessels and gangrene. We found, on the contrary, that sustained venous compression at 30 to 60 mm. of mercury for two minutes followed by a release of this pressure for an-

other two minutes resulted in the clinical benefits which we wish to report. The technic consisted of applying venous compression at mid-thigh, alternating with release in periods of two minutes for as long as twelve hours continuously each day.

The criteria employed in determining the effectiveness of treatment consisted of: (1) walking test; (The patient was required to walk at a rate of eleven paces per five seconds. The total distance and the time the patient was able to walk plus the time at which claudication developed were recorded.) (2) hot water immersion test (Landis); (3) oscillographic readings; (4) relief of pain; (5) healing of ulcers; (6) effect of treatment on skin temperature.

CASE REPORTS

CASE 1.— A. W., a forty-eight-year-old Jewish male, a salesman, married, was first seen Sept. 8, 1935, with a history of having had diabetes for thirteen years. Seven months before, in "breaking in" a pair of new shoes, he developed a blister over the medial surface of the head of the first right metatarsal, which subsequently became infected and had not healed up to the time of admission. He also complained of substernal pain on exertion and paresthetic symptoms in the plantar surface of the right foot. His diabetic management had consisted of dietetic restrictions up to seven months previously, and, after the ulcer had appeared, he was given 20 units of insulin twice a day. The treatment of the ulcer consisted of bed rest, during the major portion of this period, and at various times, baking and wet dressings.

Examination disclosed a middle-aged man, poorly nourished, presenting evidence of cataracts in both eyes. His blood pressure was 193/100 mm. The lower extremities showed the following: a small indolent ulcer one-quarter of an inch in diameter on the medial surface of the right metatarsophalangeal joint, with a grayish unhealthy base, surrounding redness, and slight edema of the right leg. No dorsalis pedis or posterior tibial pulsations could be obtained.

TABLE I A
HOT WATER IMMERSION (LANDIS)*

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	79.2° F.	80.2° F.	79.2° F.
After 20 minutes' immersion of hands in hot water (110° F.)	81.2° F.	85.7° F.	79.2° F.

*Foot temperatures in this and subsequent experiments were taken at the base of the first toe or as near that point as the lesion permitted.

TABLE I B
OSCILLOMETRIC READINGS

	LEFT LEG					RIGHT LEG				
Blood pressure	220	180	140	120	80	220	180	140	120	80
Dorsal pedis	0	0	0	0	0	0	0	0	0	0
Lower 1/3 leg	0	0	Tr	Tr	0	0	0	Tr	Tr	0
Upper 1/3 leg	0	0	Tr	Tr	Tr	0	0	Tr	Tr	0
Thigh	1	1	3/4	1/2	1/2	1/2	1/2	1/4	1/4	Tr

The diagnosis was essential hypertension, diabetes mellitus, and peripheral vascular sclerosis with partial obstruction and chronic indolent ulcer of foot.

TABLE II

	LEFT LEG								RIGHT LEG							
	220	180	160	140	120	100	80	60	220	180	160	140	120	100	80	60
Blood pressure																
Dorsal pedis	0	Tr	Tr	Tr	Tr	Tr	Tr	Tr	0	0	0	0	0	0	0	0
Lower $\frac{1}{3}$ leg	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{2}$	1	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	0	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	Tr	Tr
Upper $\frac{1}{3}$ leg	$1\frac{1}{2}$	2	2	2	1	1	1	1	0	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{3}{4}$	1	$\frac{1}{2}$	$\frac{1}{2}$
Thigh	2	2	$2\frac{1}{2}$	3	$2\frac{1}{2}$	$2\frac{1}{2}$	2	2	1	$\frac{3}{4}$	1	$\frac{3}{4}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{4}$

The patient was put to bed, with a baker over his legs at a temperature of 95° F., boric acid dressings were applied to the ulcer, and the compression-release treatment was given six hours daily. Within eight days the ulcer healed completely. Pain in the foot disappeared after the first day of treatment. On the tenth day, before discharge from the hospital, oscillographic readings were again obtained (Table II.)

It will be observed that there was a remarkable increase in the oscillographic reading. It is of interest to state that the right dorsalis pedis artery could now be palpated.

CASE 2.—D. C., sixty-three years old, Jewish male, was admitted to the hospital Aug. 14, 1935. He gave a one-year history of attacks of very painful intermittent claudication in the calf of the right leg on walking one block, which pain subsided after five minutes' rest. He smoked twenty cigarettes a day. The feet were cold, the right foot more than the left. No dorsalis pedis, posterior tibial, or popliteal pulsation was obtained in either leg.

TABLE III A
OSCILLOGRAPHIC READING—AT 120 MM.

	RIGHT LEG	LEFT LEG
Dorsalis pedis	0	0
Lower $\frac{1}{3}$ leg	$\frac{1}{4}$	$\frac{1}{2}$
Upper $\frac{1}{3}$ leg	$\frac{1}{2}$	$\frac{1}{2}$

TABLE III B
HOT WATER IMMERSION TEST (LANDIS)

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	88.5° F.	90.4° F.	85.0° F.
After 20 minutes' immersion of hands in hot water (110° F.)	91.3° F.	93.0° F.	85.0° F.

These tests indicated the existence of peripheral vascular sclerosis with partial obstruction.

Wassermann test was negative. Blood chemistry, blood count, and urinalysis were all normal. The electrocardiogram showed left axis deviation.

Before admission to the hospital, treatment consisted of rest, infra-red ray therapy, diathermy, and discontinuance of smoking. He had received intravenous hypertonic saline three times a week for two months also. There had been no improvement.

On August 15, the patient was started on venous compression treatment at 30 mm. pressure, alternating two minutes of pressure with two minutes of release for twelve hours a day with no additional form of treatment. The results are presented in the graph (Fig. 1). It will be seen that, beginning with the third day of treatment, there occurred a rapid and marked improvement in the walking ability of the patient. He reached the peak of improvement in seven days and remained at the same level, in spite of further treatment. After one week the patient was able to walk three times the control distance, and it took twice as long for claudication to appear. After three weeks of treatment, the patient stated that he was able to walk fifteen blocks before onset of pain.

It is interesting also to mention that there occurred a rise of 4.1° F. in the temperature of the involved foot after one hour of intermittent compression treatment.

The patient was then discharged for one month. At the end of that time, examination disclosed a return to his original condition. Since resuming daily treatments for two hours, he has again recovered his improved vascular capacity.

CASE 3.—W. H., thirty years old, Jewish male, was admitted June 19, 1935, with the following history: Three years before, the patient noticed a swelling on his right large toe. He consulted a physician, who operated upon him for an ingrown toenail. He remained in bed for eight months following this operation, because of pain in his foot and failure of the wound to heal. One year ago he consulted Dr. Leo Buerger, who made a diagnosis of thrombo-angiitis obliterans. He was treated for twelve weeks with slight improvement but subsequently was confined to bed for eleven months. During the preceding two months, the large toe became

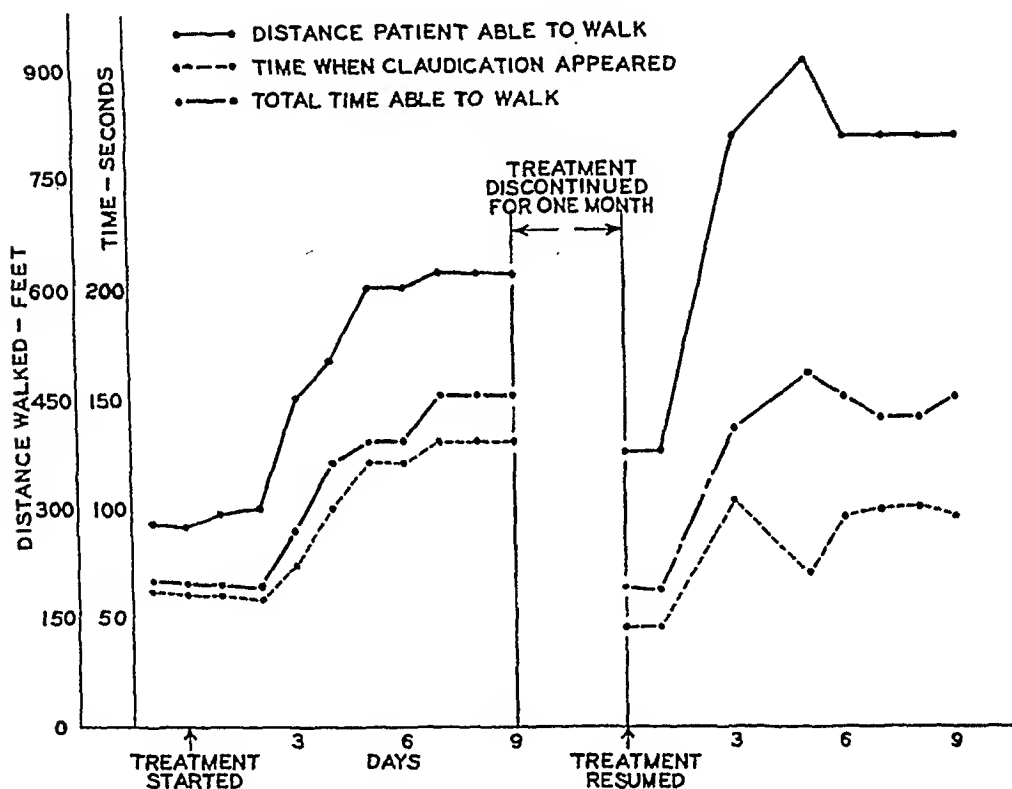


FIG. 1

progressively worse and turned black, with the bone of the distal phalanx exposed. His pain was unbearable, especially at night. He resorted to the use of large doses of codeine and aspirin for relief and, at that time, described his condition as being "only a shell of his former self." He had, up to the time of admission, smoked incessantly, twenty to thirty cigarets per day.

Examination disclosed a well-nourished male, with negative physical findings except in his lower extremities. The right foot was cyanotic and cold, and there existed a gangrenous area involving the distal half of the right great toe, with the bone of the distal phalanx exposed. There was no palpable pulsation of the dorsalis pedis, posterial tibial or popliteal arteries of either leg. The oscillometer showed no pulsations of the right lower extremity up to the lower third of the thigh. The left extremity showed an oscillometric reading of 3.5 at the lower third of the thigh but no oscillations below the knee. There was pallor on elevation and rubor on dependency in both legs, more marked on the right.

TABLE IV
HOT WATER IMMERSION TEST (LANDIS)

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	79.1° F.	81.0° F.	75.0° F.
After 35 minutes' immersion of hands in hot water (110° F.)	80.0° F.	83.4° F.	75.4° F.

The admission diagnosis was thrombo-angiitis obliterans, with osteomyelitis of the distal phalanx of the right great toe, which diagnosis was confirmed by x-ray examination. Urinalysis, blood count, blood chemistry, and Wassermann examinations were all negative. He was given the following treatments: bed rest, continuous baking at 95° F., intravenous injections of 250 c.c. of 5 per cent saline every other day, alternating with 2 e.e. of pancreatic extract (insulin-free) intramuscularly every other day, daily foot soak at 95° F. for twenty minutes; smoking was promptly and completely stopped.



Fig. 2.

In spite of all this extensive therapy, the gangrene advanced to involve the entire great toe plus the second and third toe, and two weeks later the entire distal half of the foot was gangrenous (Fig. 2). His pain was intense and required 8 grains of codeine, 40 grains of aspirin and one-half pint of whisky per day for partial relief.

On July 21, one month after admission, all treatments were stopped except the baking, and the intermittent venous compression machine was applied, using 25 mm. of mercury pressure for two minutes alternating with two minutes of release for twelve hours daily. Within twenty-four hours, there was a marked relief of pain. The patient now required only 1 grain of codeine a day for complete relief.

Observations on several successive days showed that the blueness of the foot was fading and that the patient was very comfortable. On the sixth day of treatment, the patient stated that he had had the most comfortable night since his stay in the hospital. After eight days of treatment, several small islands of granulation tissue appeared in the margin of the gangrenous lesion, and the next day

bleeding was observed. Two weeks later the machine was stopped for three days, during which time the patient again complained continuously of very severe pain which was immediately relieved upon the resumption of treatment with the machine.

On August 15, the Landis immersion test produced no rise in temperature with the hands in hot water. The oscillometric reading was one-quarter in the upper third of the right leg at 120 mm. of pressure. Readings distal to this were all zero.

On August 17, it was decided that the patient's period of illness should be shortened by amputating the gangrenous portion of the foot. Although the surgeon expressed the opinion that the point of amputation was indicated at mid-thigh, we prevailed upon him to amputate above the ankle, since all clinical signs pointed to an improved circulation since the introduction of intermittent venous compression. The amputation was performed 2 inches above the malleoli. It was observed at the operation that, on incision through the soft parts, there was considerable ooze, requiring the use of hemostatic clamps. When the anterior and posterior tibial arteries were cut, no bleeding occurred. The arteries were completely occluded by organized thrombi. It was obvious that all this unusual bleeding came from the increased collateral circulation. The toxic temperature immediately subsided, and one week later the patient was discharged from the hospital with the wound healed by primary union.

CASE 4.—J. F., fifty-three years old, Italian male, a porter, first came under observation March 25, 1932, with a history of diabetes of four years' duration. He had been on a diet with insulin for one year. Three months before he had begun to complain of pain in his right foot, coldness, and claudication on walking. One month before, a painful ulcer had appeared on the right large toe which had since refused to heal. Examination disclosed, besides his diabetes, characteristic evidence of severe peripheral vascular sclerosis of both legs, worse in the right. No palpable pulsations were obtained in dorsalis pedis or posterior tibial arteries of either leg. The oscillometric reading was zero in the lower third of the legs. There was an unhealthy appearing ulcer on the medial surface of the terminal portion of the right large toe. He was treated with bed rest, contrast baths, continuous baking, foreign protein, and injections of 300 c.c. of 5 per cent saline intravenously three times a week for six months. The ulcer healed completely in this period. Oscillometric studies on discharge showed traces of oscillations in the lower one-third of his legs. It is interesting that a growth of entirely new toenails occurred, indicating apparent improvement in nutrition of the tissues.

Three years later, the patient appeared with another ulcer on the medial surface of the tip of the right second toe. Examination, this time, disclosed evidence of progressive peripheral sclerosis since the last visit. The ulcer was extremely painful, especially at night, and necessitated the daily use of 4 grains of codeine. The patient was placed on the following regime: 300 c.c. of 5 per cent saline intravenously every other day, continuous baking, bed rest, daily warm baths, and frequent use of wet dressings. At the end of five months the foot was still painful and no healing had occurred—a response vastly different from that in our former experience with him. The results of functional tests made at this time are given in Table V.

TABLE V

HOT WATER IMMERSION TEST (LANDIS)

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	81.0° F.	82.4° F.	80.6° F.
After 30 minutes' immersion of hands in hot water (110° F.)	81.4° F.	84.9° F.	80.6° F.

Oscillometry showed no oscillations up to the knee. X-ray films showed calcification of blood vessels in his feet. There was no bleeding from the ulcer.

All previous treatment was stopped, and he was treated with the compression-release machine at 60 mm. of pressure for two hours daily. Within five days the pain had entirely disappeared. The patient stated that he had a sense of warmth in his feet, and he slept without medication. The walking test showed startling improvement in the functional capacity of his vessels (Fig. 3). At the end of two weeks of treatment, the ulcer showed clear evidence of healing. Probing the sinus produced marked bleeding in spite of the fact that oscillometric readings remained 0. The patient was not confined to bed. Three weeks later x-ray films showed an osteomyelitis of the terminal phalanx. Local amputation of the toe was performed and the stump healed in two weeks.

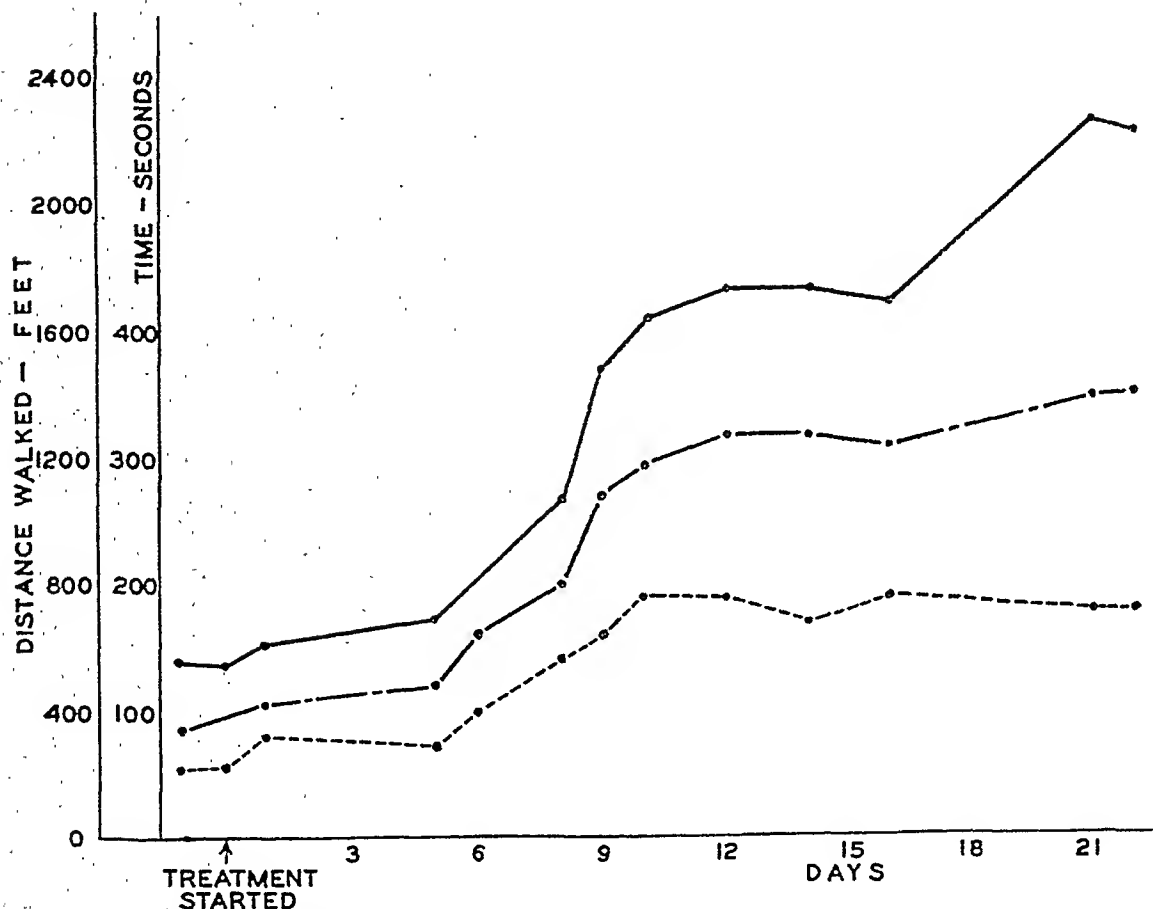


Fig. 3.—●—● Distance patient was able to walk.
 ● - - ● Time when claudication appeared.
 ● — ● Total time patient was able to walk.

CASE 5.—B. S., a fifty-seven-year-old Jewish male, was admitted to the hospital Sept. 2, 1935, with the following history: He had had a mild form of diabetes for ten years, adequately controlled with slight dietetic restrictions. Since the age of thirty years, he had had difficulty with his lower extremities. For the past ten years, he had had intermittent claudication and complained that his feet were continually cold. Three weeks before admission, he sustained a burn from a hot water bag on the outer surface of his left small toe. It rapidly became infected, and, in four days, this toe became gangrenous. The infection spread to involve the outer distal half of his left foot. He had fever for ten days. Examination disclosed an acutely ill male, temperature 102.6° F. There was a gangrenous ulcer at the base of the left small toe three-quarters of an inch in diameter. The toe itself was black. The dorsal and lateral surfaces of the fourth toe were also gangrenous. The foot was edematous, and lymphangitic streaks extended up to

the middle of the leg. Vascular studies on extremities showed no pulsations obtained in dorsalis pedis, posterior tibial, or popliteal arteries of either leg; oscillometric readings were zero below the knees.

TABLE VI
HOT WATER IMMERSION TEST (LANDIS)

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	82.9° F.	82.0° F.	75.0° F.
After 30 minutes' immersion of hands in hot water (110° F.)	86.0° F.	82.8° F.	75.5° F.

The Wassermann test was negative. The blood count showed 23,400 white blood cells, with 84 per cent polymorphonuclear leucocytes. Urine showed traces of



Fig. 4.

Fig. 5

sugar, and blood sugar was 131 mg. per cent. The diagnosis was diabetes and peripheral vascular sclerosis with infected gangrene, involving the two lateral toes of the left foot.

For one week, he was treated with wet dressings and baking. The gangrenous lesion continued to spread and to involve the third left toe. His temperature ran a septic course. He complained of a great deal of pain and required the frequent administration of large doses of morphine, codeine, and aspirin. This period was used as a control period.

On the eighth day, venous compression at 60 mm. of mercury and release were started for three hours a day.

Within twenty-four hours, his temperature had subsided, and his pain had almost entirely disappeared. The lesion rapidly became localized. The necrotic slough was removed, and the gangrenous toes were disarticulated without touching the viable tissue. Forty-eight hours after treatment had been started, granulation tissue began to appear on the outer margin of the gangrenous ulcer (Fig.

4). Within a week, the granulation tissue had covered the heads of the exposed metatarsal bones. Within two months all the remaining toes underwent spontaneous amputation and the patient was left with a painless, healthy, granulating stump. At the end of four months of treatment, skin had grown over one-half of the ulcer (Fig. 5).

It is interesting to note that the patient complained of pains and paresthesias in the toes of the uninvolved foot. After two days of compression treatment of this leg, these symptoms promptly disappeared.

CASE 6.—F. S., sixty-four years old, Jewish, a presser by occupation, was admitted on Aug. 30, 1935. He stated that for the five previous months he had had pain in the right calf on walking one block. His feet felt cold. Lower extremities showed the following: feet cold, no dorsalis pedis pulsation obtained in the right foot, but faint pulsations present in the left. X-ray examination showed calcification of blood vessels of both legs and feet. Blood pressure was 162/98.

TABLE VII A
OSCILLOMETRIC READINGS (MAXIMUM AT 140 MM.)

	RIGHT	LEFT
Foot	0	0
Above ankle	0	0
Below knee	0	0
Above knee	$\frac{1}{2}$	1

TABLE VII B
HOT WATER IMMERSION TEST (LANDIS)

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	81.2° F.	82.1° F.	79.2° F.
After 30 minutes' immersion of hands in hot water (110° F.)	83.9° F.	85.5° F.	79.3° F.

Functional walking test showed that he was able to walk 547 feet at eleven paces per five seconds. Pain occurred in 70 seconds, and he ceased walking in 90 seconds. The diagnosis was peripheral vascular sclerosis with partial obstruction and functional incapacity.

He was treated with alternating venous compression and release at 20 mm. of mercury for one hour three times a week and was then admitted to the hospital, where he was given this treatment twelve hours every day for twelve days. The results are seen in Fig. 6. It will be observed that the patient showed a definite increase in walking ability after twelve days of treatment.

A note of interest is the observation that the skin temperature rose 4.2° F. after one hour of treatment.

TABLE VIII
SKIN TEMPERATURE

	BASE OF RIGHT GREAT TOE	BASE OF RIGHT FOURTH TOE	BASE OF LEFT GREAT TOE	BASE OF LEFT FOURTH TOE
Before treatment	79.2°	79.8°	80.2°	81.5°
After treatment for one hour with alternating venous compression and release	83.0°	83.8°	84.8°	85.6°
Total rise	3.8°	4.0°	4.6°	4.1°

It is interesting, also, that although he had difficulty in walking from the subway to the hospital for treatment, he was able to walk back the same distance with ease after treatment.

CASE 7.—H. G., fifty years old, male, Jewish, was admitted on Sept. 24, 1935, with a history of having trimmed a callus on his right large toe four months before. The toe had become infected, swollen, painful, and had begun to discharge pus. He had treated the toe with local antiseptics and wet dressings. At the end of two months, his physician had discovered that the patient was diabetic. He had immediately been given a diet and 35 units of insulin a day. Despite continuous treatment with baking, wet dressings, and bed rest, his toe became steadily worse, and he was referred to the hospital. On examination he was found to have a sinus tract arising from an ulcer one-half inch in diameter on the medial surface of the right great toe and extending approximately one inch into the deeper structures.

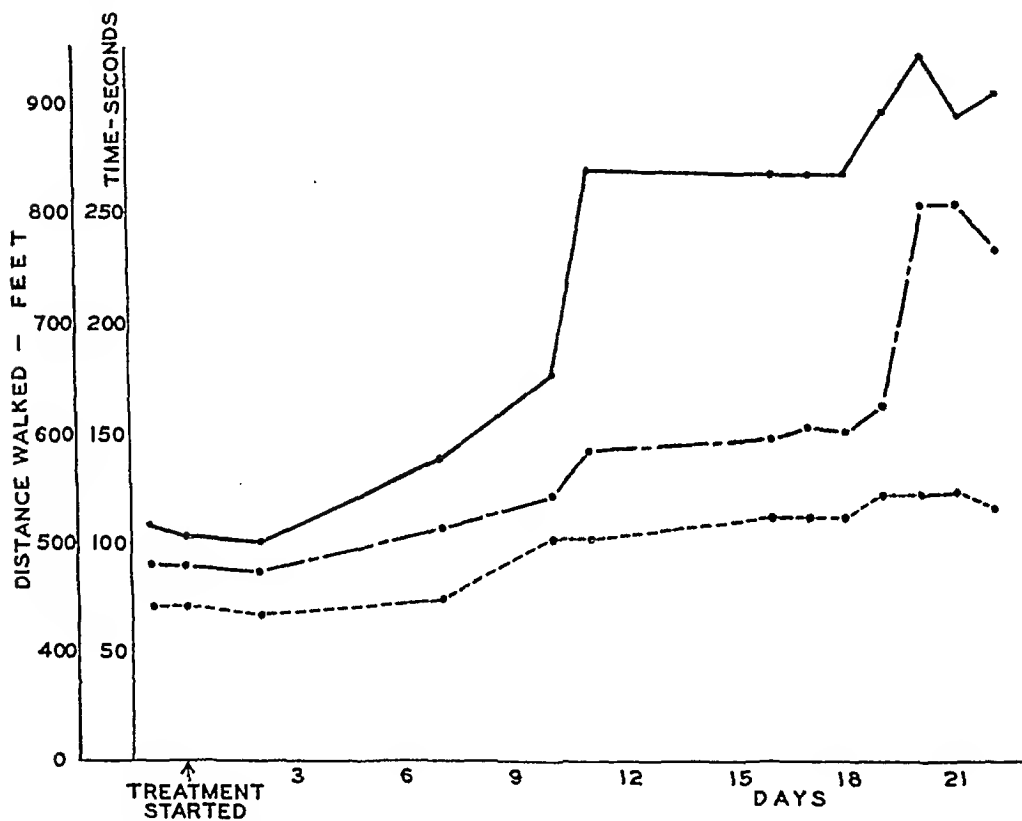


Fig. 6.—●—● Distance patient was able to walk.
 ●---● Time when claudication appeared.
 ●—● Total time patient was able to walk.

Probing the sinus gave a sensation of grating bone. There was no bleeding. The toe was painful, swollen, red, edematous, and very tender to touch. X-ray examination showed osteomyelitis of the base of the proximal phalanx and marked calcification of the vessels of both feet. Results of the vascular study on admission are given in Table IX, A and B.

TABLE IX A
HOT WATER IMMERSION TEST (LANDIS)

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	81.4° F.	83.6° F.	77.6° F.
After 30 minutes' immersion of hands in hot water (110° F.)	84.0° F.	87.6° F.	77.8° F.

TABLE IX B.
OSCILLOMETRIC READINGS

	RIGHT LEG								LEFT LEG							
	220	200	180	160	140	120	100	80	220	200	180	160	140	120	100	80
Blood pressure																
Dorsal pedis	0	0	0	0	0	0	0	0	0	0	0	0	0	Tr	Tr	1/4
Lower 1/3 leg	0	0	0	Tr	1/4	1/4	Tr	Tr	0	0	0	0	1/4	1/4	1/4	1/4
Upper 1/3 leg	0	Tr	1/4	1/4	1/2	3/4	1/2	1/2	0	1/2	3/4	3/4	1	2 3/4	2 3/4	2 3/4
Above knee	4 1/2	3 1/2	3 1/2	3	3	2 1/2	2	2	3 1/2	4 1/2	5	5	4	3 1/2	2 1/2	1 1/2

TABLE X

	RIGHT LEG								LEFT LEG							
	220	200	180	160	140	120	100	80	220	200	180	160	140	120	100	80
Blood pressure																
Dorsal pedis	0	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{3}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{3}{4}$	$\frac{3}{4}$	1	$\frac{3}{4}$
Lower $\frac{1}{3}$ leg	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{3}{4}$	$\frac{3}{4}$	$\frac{3}{4}$	$\frac{3}{4}$	$\frac{1}{2}$	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	2	2
Upper $\frac{1}{3}$ leg	2	2	$2\frac{1}{2}$	3	3	5	5	3	$1\frac{1}{2}$	2	$2\frac{1}{2}$	$3\frac{1}{2}$	$3\frac{1}{2}$	4	$3\frac{1}{2}$	2
Above knee	$2\frac{1}{2}$	$3\frac{1}{2}$	$4\frac{1}{2}$	5	5	5	5	5	$1\frac{1}{2}$	$2\frac{1}{2}$	3	$3\frac{1}{2}$	$3\frac{1}{2}$	3	$2\frac{1}{2}$	2

The diagnosis was peripheral vascular sclerosis with marked obstruction, osteomyelitis, and diabetes.

Treatment was started with venous compression at 30 mm. of mercury alternating with release, two minutes on and two minutes off, for ten hours daily.

Within twenty-four hours the pain had disappeared. Five days after the onset of treatment, a dorsalis pedis pulse was obtained, and, on probing, profuse bleeding occurred. Oscillometric readings are given in Table X.

There was clear evidence that a marked improvement in vascularity had occurred. It was then decided that the sinus should be exposed and the infected bone curetted. At the operation, bleeding was so profuse that it could be controlled only with hemostatic clamps. The compression treatment was continued after operation. Temperature remained normal. There was no pain. The discharge from the wound was purulent and bloody. At the end of one week, probing disclosed the existence of necrotic bone, which was removed. Two weeks later, a healthy, vascular, granulating wound was present.

CASE S.—F. C., a sixty-year-old Jewess, was admitted April 26, 1935, with a history of diabetes of twelve years' duration. One year before she had begun to complain of pain and coldness in the right foot, worse on walking. Six weeks ago, an ulcer, which became progressively larger, appeared on the dorsum of the foot. Examination disclosed an aged woman, poorly nourished, with evidence of marked, generalized atherosclerosis. Her blood pressure was 164/90. On the dorsum of the right foot was a large gangrenous area, 2 inches in diameter, sharply demarcated, with surrounding redness. The gangrenous skin was dry and leathery. There were lymphangitic streaks extending to the upper third of the leg. Vascular study showed the following: no dorsalis pedis, posterior tibial, or popliteal pulsation in either leg. Both feet were cold.

TABLE XI A
HOT WATER IMMERSION TEST (LANDIS)

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	79.2° F.	79.6° F.	76.8° F.
After 30 minutes' immersion of hands in hot water (110° F.)	79.5° F.	79.9° F.	76.8° F.

TABLE XI B
OSCILLOMETRIC READINGS

	RIGHT LEG	LEFT LEG
Foot	0	0
Lower $\frac{1}{3}$ leg	0	0
Upper $\frac{1}{3}$ leg	0	1.5
Mid-thigh	0.5	3.0

There were obvious signs that the patient was suffering from a severe form of peripheral vascular sclerosis and a gangrenous ulcer, with secondary infection.

She was put to bed; a continuous boric acid dressing was applied to the lesion; and a baker over both legs was maintained at a temperature of 95° F. In four days the evidence of infection had subsided, and the wet dressings were discontinued. Besides exposing the lesion to dry heat, she was given daily intravenous injections of 150 c.c. of hypertonic saline, at first in 3 per cent concentration but later in 5 per cent.

Her diabetes was mild and was easily controlled with a diet consisting of carbohydrate, 175 gm.; protein, 60 gm.; fat, 100 gm.; and with 5 units of insulin t. i. d.

She was treated for two months in this fashion without making any progress. Her pain was continuous, but worse at night, and she required the daily use of from 6 to 10 grains of codeine. The patient decided to return home because of her very slight improvement. Two weeks later she returned to the hospital because her pain was unbearable. Examination disclosed an exacerbation of the infection, with redness and edema surrounding the ulcer. Her temperature was now 103° F. Blood count showed 12,900 white blood cells and 88 per cent polymorphonuclear leucocytes. A boric acid dressing was reapplied, and her legs were placed under a baker. In addition, the intermittent venous compression machine was applied at 60 mm. of mercury for five hours a day. Within twenty-four hours her pain had almost completely subsided. Within three days, the infection was controlled, and the wet dressings were stopped.

After two weeks of treatment, the Landis immersion test showed a rise of 1.7° F. of temperature in the involved foot, and the oscillometer readings showed a faint oscillation in the upper third of the leg. The ulcer was stationary in size, and, on raising the edge of the leathery skin, the margin of the ulcer appeared healthy. The surgeons, however, basing their judgment on past experiences with diabetic patients over sixty years of age who have such advanced form of arterial sclerosis and extensive gangrenous lesions, decided to amputate her leg at mid-thigh. We prevailed upon them at least to attempt an incision in the lower third of the leg and, if sufficient bleeding did not occur, then to proceed to a mid-thigh amputation. The leg incision showed a remarkable flow of blood, and the amputation was completed at that level. The main arterial trunks were completely occluded both by calcification and thrombosis, but blood flowed continuously from the soft tissues. The surgeon stated that he had never seen so much free bleeding in the presence of such severe arterial obstruction. He applied a mild compression bandage and sent the patient back to bed. For forty-eight hours so much bleeding occurred that the surgeon found it necessary to pack the stump three times in this period. Seven days after operation, the patient developed a Welch bacillus infection, from which she died in three days.

SUMMARY

The use of a new device for the clinical application of the phenomenon of reactive hyperemia by alternating venous compression with release is described. It appears, from this preliminary study, to have the following effects in the treatment of organic peripheral vascular obstruction: (1) relief of pain; (2) increase of skin temperature of extremity; (3) increase in walking efficiency; (4) increase in vascularity, permitting amputation at lower levels; and (5) healing of chronic indolent ulcers associated with vascular obstruction.

We wish to thank Dr. Henry Joachim, the chief of the medical service, for his kind cooperation.

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AN APPARATUS FOR THE PRODUCTION OF INTERMITTENT VENOUS COMPRESSION IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE*

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EVIDENCE has been presented by Lewis and Grant¹ to show that alternating venous occlusion and release result in an increase in circulation to an extremity.

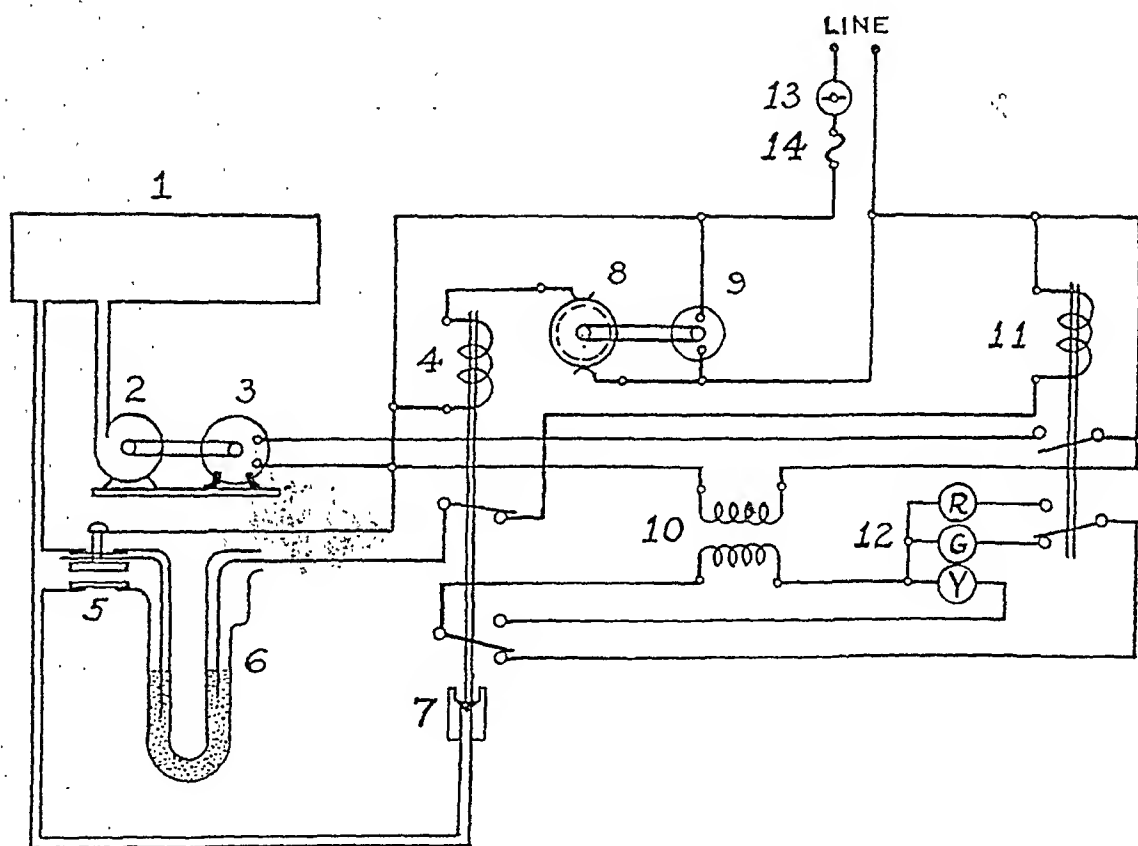


Fig. 1.—Diagram of apparatus: 1, Pneumatic cuff; 2, compressor; 3, motor; 4, relay; 5, pressure adjustment; 6, mercury manometer; 7, exhaust valve; 8, timing disk; 9, synchronous motor; 10, transformer; 11, relay; 12, indicator lights; 13, switch, and 14, fuse.

In the preceding article, the authors have given an historical survey of the use of the principle of venous compression and a preliminary report of their experience of its application in seven cases. This article is concerned with a description of the apparatus and its method of application in the treatment of peripheral vascular disease.

The apparatus consists of a motor-driven pump which supplies air to a pneumatic cuff. The pressure of this device is regulated by means of a pressure-measuring indicator. A pressure of 40 mm. of mercury is im-

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posed on the proximal portion of the diseased extremity and results in a restriction of the returning venous blood. This pressure is applied at a level which does not interfere with arterial filling. It was during the period of compression that Lewis and Grant noticed the development of active arteriolar vasodilation.

A suitable timing mechanism is incorporated in the device which maintains the pressure for two minutes, after which a release valve is actuated electrically to cause an automatic deflation of the cuff. It is during the release period that an increased arterial flow through the extremity occurs. Although Lewis and Grant produced an increase of inflow blood of as great as 600 per cent when venous compression was maintained at 90 mm. of mercury for fifteen minutes, we have found in our experimental observations in the treatment of peripheral vascular

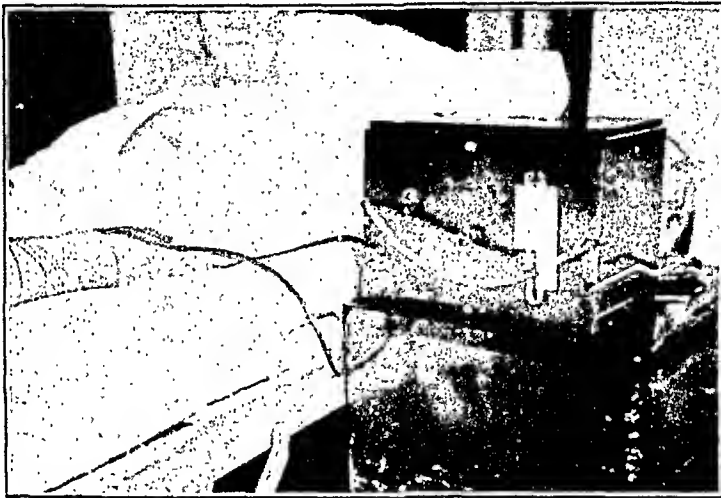


Fig. 2.

disease that a compression of 40 mm. of mercury for two minutes alternating with a similar period of release was much more satisfactory. When, however, no ulcer or gangrene is present and the outstanding symptom is intermittent claudication, pressure up to 90 mm. may be applied. With this routine it has been possible to produce alleviation of pain and increase vascular capacity as determined by functional tests in cases of organic peripheral vascular disease both in gangrenous and nongangrenous cases.

A diagrammatic illustration of the instrument is given in Fig. 1, and the manner of its application is shown in the accompanying photograph (Fig. 2).

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AURICULAR SOUND*

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THE proof that the contraction of the auricles is able to produce an acoustic phenomenon with the characters of a sound, dates from the last century and was determined by simple auscultation (Williams,¹ Stokes,² Chauveau³) in cases in which the contraction of the auricles was not followed by the corresponding ventricular contraction. Simple listening also permitted the recognition of auricular sound in other conditions, but its genesis and effects could not be recognized until the graphic records of the heart sounds simultaneously with that of other manifestations of the heart's activity, such as electrocardiogram or phlebogram, came into use.

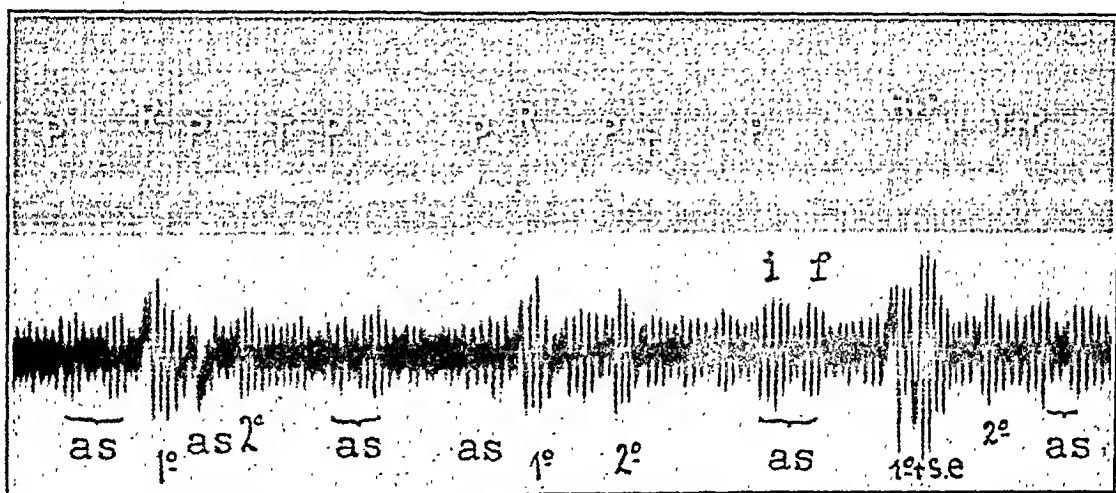


Fig. 1.—Graphic record of the auricular sound (*as*) in a case of complete heart-block; *i*, initial part; *f*, final part; *1°* + *s.e.* summation of the sound produced at the beginning of ventricular systole with the auricular sound.

The object of the present paper is merely to show synthetically and in a somewhat schematic way, some of the verified acquisitions of knowledge concerning the auricular sound obtained from the graphic record of the heart sounds. The knowledge of those facts and of their detection by the graphic method teaches the examiner to recognize these phenomena merely by listening at the precordium. The reader who desires further details concerning the auricular sound can find sufficient information in the references.

DEFINITION AND GENESIS

We must understand as the auricular sound the acoustic phenomenon produced by the contraction of the auricles, whether this be the result

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of sinus activity (Fig. 1) or of the condition called auricular flutter (Fig. 2). The graphic record of the heart sounds obtained over the precordium (Lewis,⁴ Selenin and Fogelson,⁵ Cossio,⁶ Cossio and Braun Menendez⁷) or through a detector introduced into the esophagus (Benjamin,⁸ Braun Menendez and Taquini⁹) shows that the auricular sound is formed by two groups of small oscillations, the second appearing a few hundredths of a second after the first (Fig. 1). As each group of oscillations corresponds to a different sound, we must regard the auricular sound as really formed by two different sounds which are perceived as one only because of the deficiency of the human ear as an acoustic receptor.

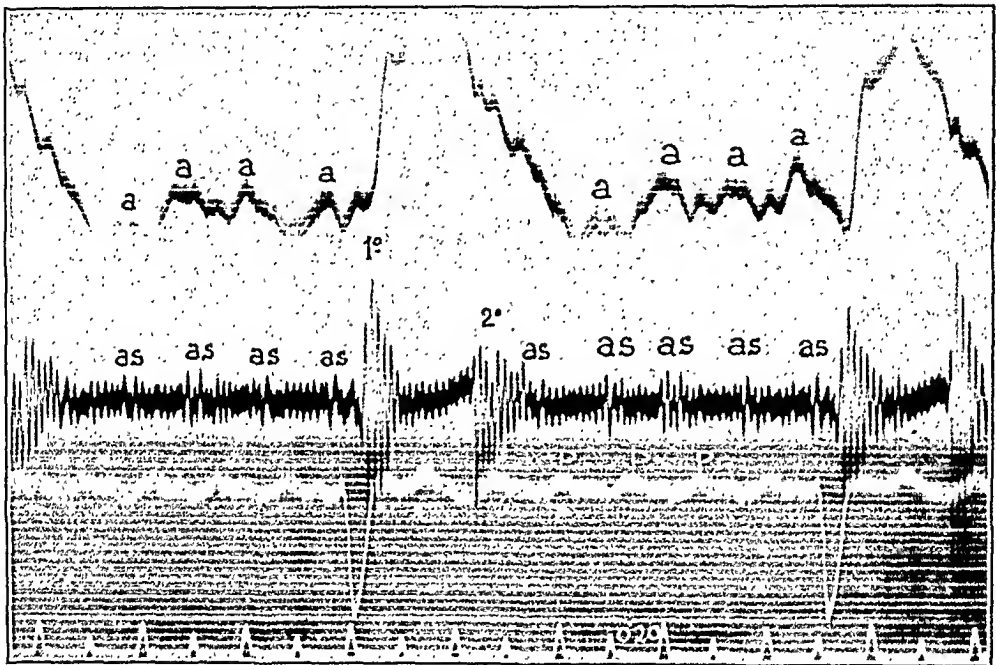


Fig. 2.—Graphic record of auricular sound (as) in a case of auricular flutter with complete heart-block. Above, optical record of venous pulse.

The verification that the first group of oscillations of the auricular sound (Cossio and Braun Menendez⁷) is produced during the height of the auricular systole, i.e., when the tension of the auricular walls and the compression of the blood they contain are maximum, shows that the first part or initial portion of the auricular sound is due equally to the vibrations of the auricular walls set in tension and to the vibration of the mass of blood they include and compress, as had been previously hinted by Lewis.⁴ The proof that the second group of oscillations of the auricular sound occurs once the auricular systole is finished has induced the idea that the second or final part is due to the vibrations that appear as a consequence of the auricular systole—tension of the ventricular walls produced by the blood expelled into them by the auricular systole

or vibration of the auriculoventricular valves. Because of those two anatomical factors, the auriculoventricular valve is the one more fit to vibrate and generate a sound (Dock¹⁰), it is natural to attribute the second part of this sound to the tension of this valve and not to the vibration of the ventricular myocardium (Lewis¹ and Cossio and Lascalea¹¹). In support of this view is the fact that the second part of the auricular sound is produced at the moment the auriculoventricular valve is higher and, therefore, when its tension is greatest. The different origin of the initial and the final parts of the auricular sound explains the dis-

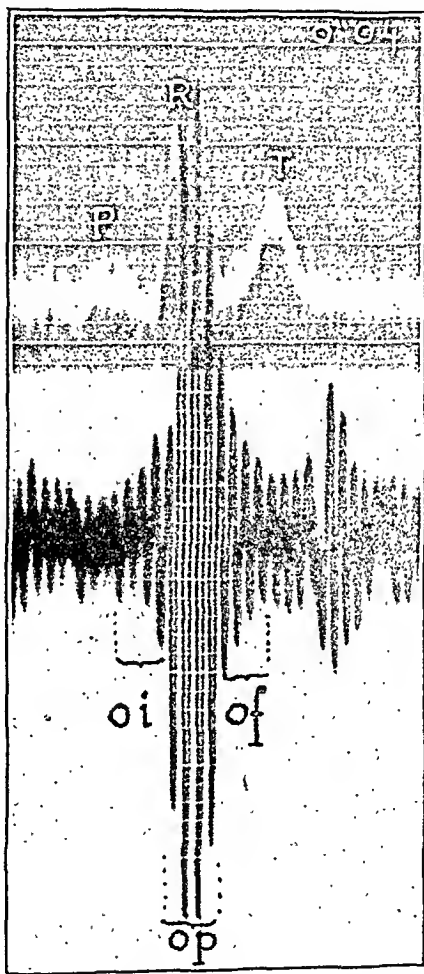


Fig. 3.—Graphic record of first heart sound in normal conditions; *oi*, initial oscillations; *op*, principal oscillations; *of*, final oscillations.

crepancy between its features when detected through the esophagus and over the precordium. When the auricular sound is elicited through the esophagus, it is its initial portion that is more constant and predominates in the record. This is due to the fact that this initial portion is generated, as we have stated, in the walls of the auricles, and these are situated in intimate contact with the esophagus. On the contrary, when the auricular sound is elicited over the precordium, it is the second part of the sound that predominates because of its origin in the ventricles in close contact with the thoracic wall.

THE AURICULAR SOUND IN NORMAL CONDITIONS

The graphic record of the heart sounds obtained simultaneously with the electrocardiogram or the phlebogram, especially the former, has shown that normally the auricular sound as detected over the precordium is one of the normal constituents of the first heart sound (Cossio and Lascalea¹¹) or it presents itself as an independent sound (Bridgman,¹² Wolferth and Margolies,¹³ Brann Menendez and Orias¹⁴), producing the condition called physiological reduplication or splitting of the first heart sound (Cossio,⁶ Cossio and Braun Menendez¹⁵).

Auricular Sound and First Heart Sound.—In normal conditions each auricular contraction is followed almost immediately by its corresponding ventricular contraction. This accounts for the fact that the second part of the auricular sound is produced just before the sound generated

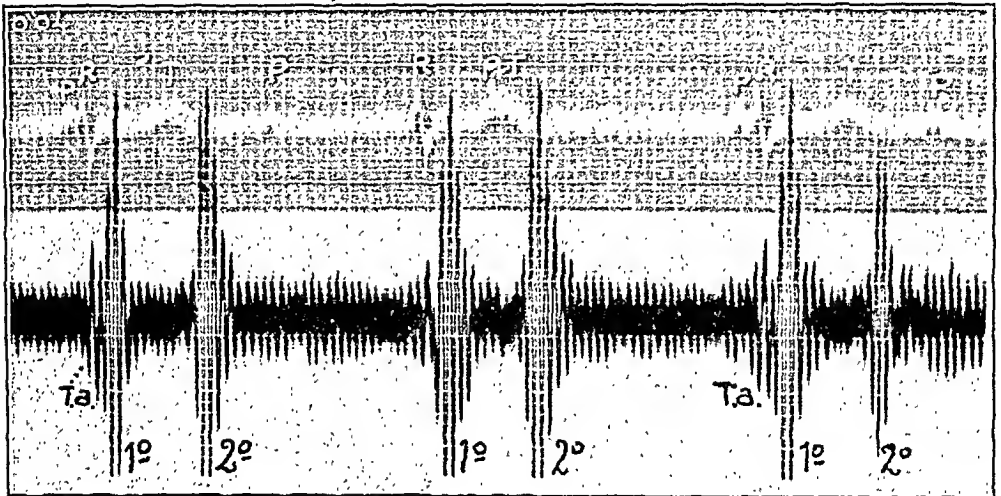


Fig. 4.—Graphic record of the first heart sound with and without the corresponding precedent auricular contraction. The first heart sound has initial oscillations only when the contraction of the ventricles is accidentally preceded by the contraction of the auricles, showing that the initial oscillations of the first heart sound are due to nothing but the auricular sound.

by the auriculoventricular valve when it is put into tension at the beginning of the ventricular systole. The lack of demarcation between those two acoustic phenomena, namely, the final portion of the auricular sound and the initial portion of the sound due to the ventricular systole, causes both to form the single sound called "first heart sound" (Figs. 3 and 4). In other words, the acoustic phenomenon called the "first heart sound" is formed by the succession of two acoustic phenomena produced so closely one to another that they are perceived as one sound.

Auricular Sound and Physiological Reduplication or Split First Heart Sound.—The better transmission of the auricular sound from its place of origin to the precordium, as takes place frequently in childhood (Bridgman¹²), causes it to be perceived as an individual sound, independent of the sound produced by the closure of auriculoventricular

valves. The greater original intensity of the auricular sound, as a consequence of a more lively contraction of the auricles, as happens in the case of overactivity of the heart (emotion or muscular exercise) or at

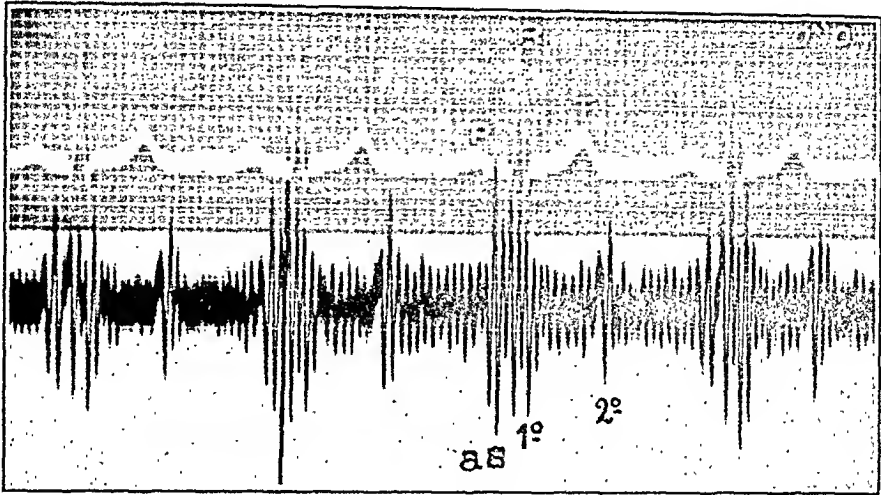


Fig. 5.—Constant reduplication of first heart sound in a healthy person. The auricular sound (*as*) of unusual size appears as an independent acoustic phenomenon, without any relationship to the sound produced at the start of the ventricular systole. That the oscillations *as* are nothing else than the auricular sound is established because it precedes the QRS complex of the electrocardiogram obtained simultaneously.

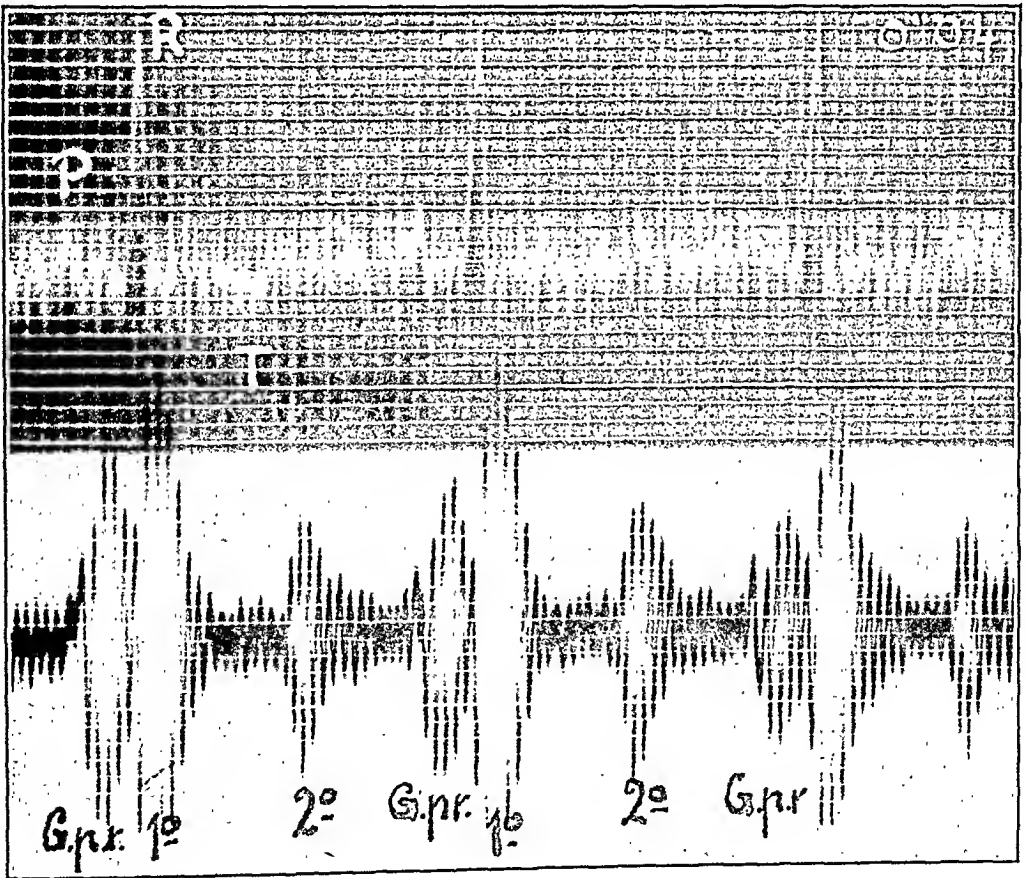


Fig. 6.—Reduplication of first heart sound with a certain cadence of presystolic gallop rhythm in a case of arterial hypertension without heart failure. The sound marked with the letters *G. pr.* precedes the QRS complex and represents an auricular sound of unusual degree.

the end of the expiration (Cossio and Braun Menendez¹⁵) causes also the auricular sound in the precordium to appear as an individual, isolated sound, independent of the one due to the ventricular systole.

The existence of an auricular sound as an individual acoustic phenomenon independent of the sound that appears at the beginning of the ventricular systole causes the presence of two successive sounds: one produced in the auricles and the other in the ventricles, in place of the normal single sound called "first heart sound." This results in the condition known as reduplicated or split first heart sound, according to the degree of separation of the two successive sounds (Fig. 5).

THE AURICULAR SOUND IN ABNORMAL CONDITIONS

The auricular sound appears over the precordium as an isolated acoustic phenomenon in many abnormal conditions. These conditions

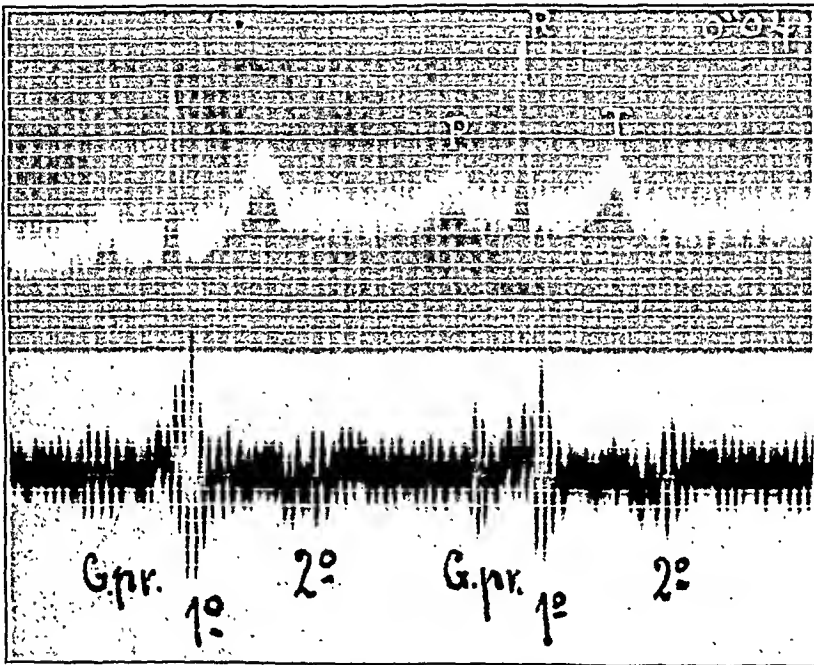


Fig. 7.—Presystolic gallop rhythm produced by the auricular sound (*G. pr.*) independent of the sound produced at the beginning of the ventricular systole. The independence of the auricular sound is due to the increase of the time of the auricular ventricular conduction ($P-R = 0.22$).

must be considered under two different circumstances. First, when each auricular systole is followed by its respective ventricular systole (sinus rhythm) and, second, when the contraction of the auricles becomes independent of that of the ventricles (complete heart-block).

Sinus Rhythm.—The auricular sound exists as an independent phenomenon without relation to the sound produced at the beginning of the ventricular systole, though each auricular contraction is followed by its corresponding ventricular contraction, in the following conditions: (a) increased energy in the auricular contraction; (b) delay in the conduction of the stimulus from auricles to ventricles; and (c) delayed appearance of the sound produced at the onset of ventricular systole.

When the greater energy of the auricular systole causes a more intense auricular sound, it appears as an isolated phenomenon, independent of the sound produced at the beginning of the ventricular systole. The position of this auricular sound in relation to the initial ventricular sound, and influenced by the heart rate, determines whether it is spoken of as reduplication of the first heart sound or as a presystolic gallop rhythm. Both conditions are found in arterial hypertension (Routier and Van Bogaert,¹⁶ Cossio⁶), in mitral stenosis (Lewis¹⁷), and in aortic

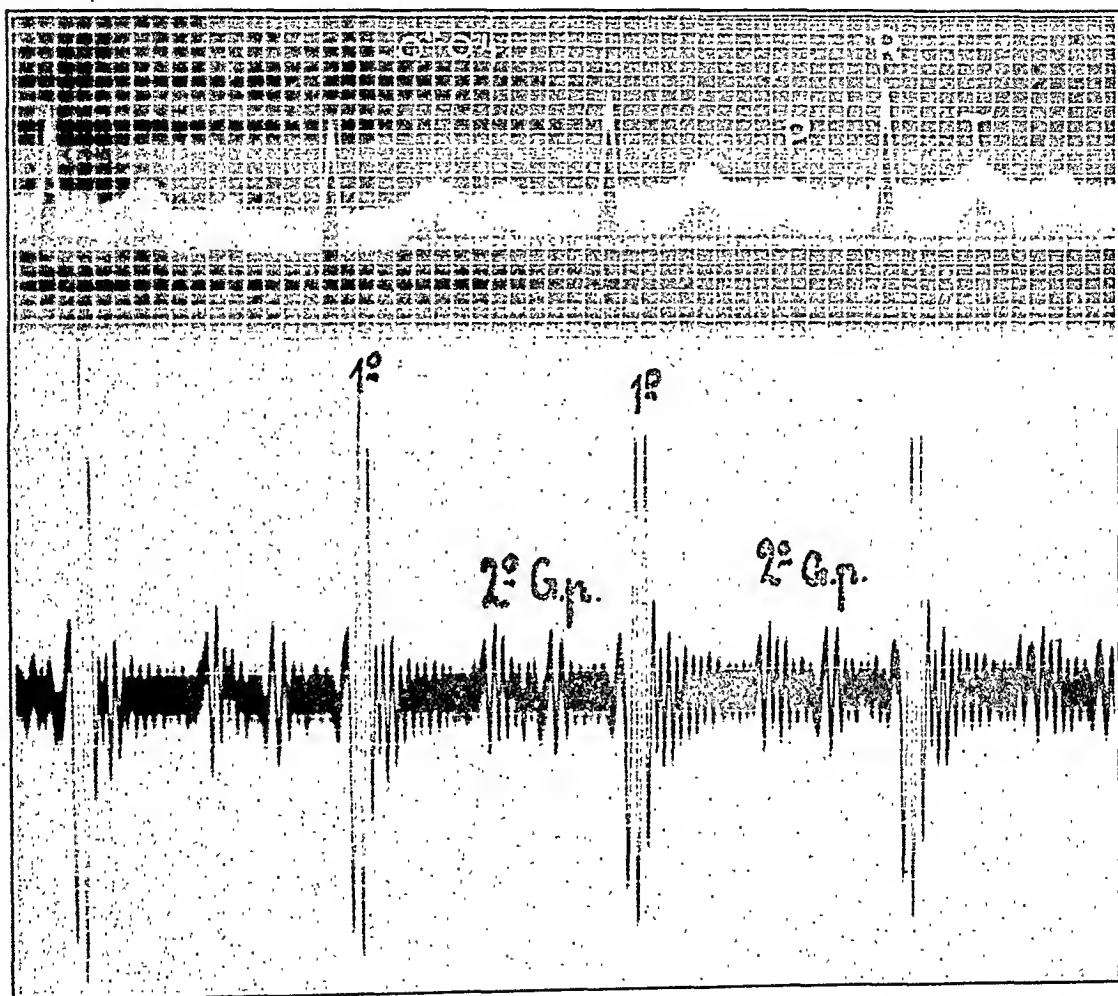


Fig. 8.—Graphic record obtained of the same patient as Fig. 7 but with greater delay of auricular ventricular conduction ($P-R = 0.26$). Now the auricular sound is situated at the beginning of diastole ($G. p.$).

insufficiency (Laubry and Pezzi¹⁸)—states in which for various reasons the auricular contraction is more lively and generates a stronger auricular sound (Fig. 6).

A moderate delay of the auriculoventricular conduction means an increased interval between auricular and ventricular systole. The final portion of the auricular sound, which in normal conditions forms part of the first heart sound, separates itself from the other component of the first sound, which is produced at the start of the ventricular systole. In this case there are two successive sounds, i.e., the condition called

reduplicated first heart sound or presystolic gallop rhythm, according to the cadence; and those two sounds are due to a disturbance of the auriculoventricular conduction (White,¹⁰ Cossio⁶). If this delay in the conduction is conspicuous, the auricular sound instead of being situated

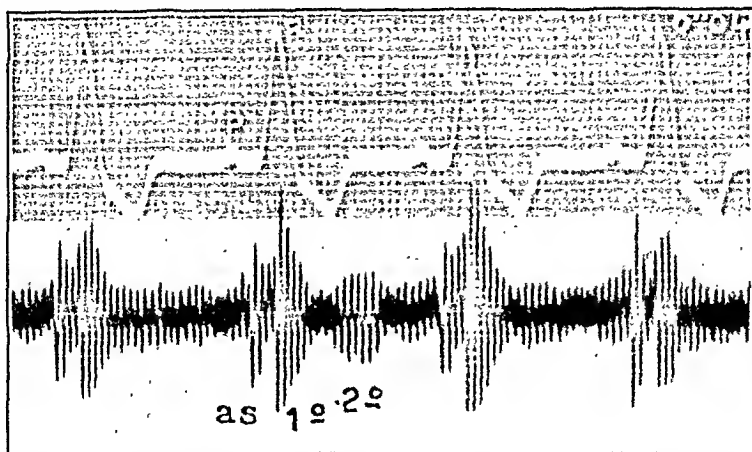


Fig. 9.—Permanent reduplication of first heart sound in a patient with bundle-branch block. In this case the reduplication is due to the independence of the auricular sound (*as*) caused by the delay of the sound produced at the beginning of the ventricular systole (*1°*) as a consequence of the disorder in intraventricular conduction.

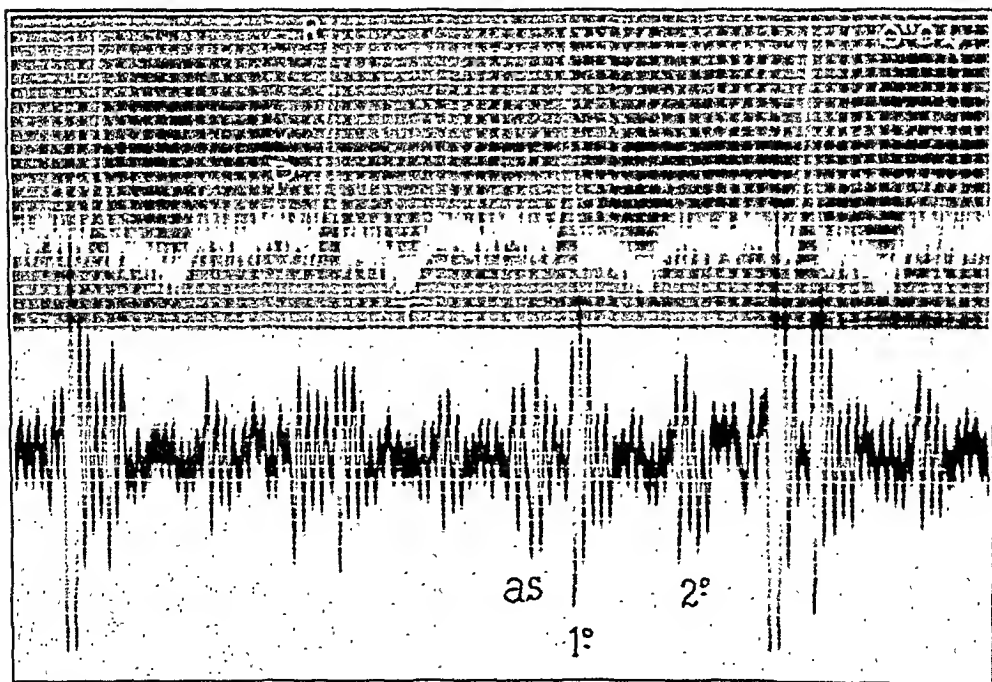


Fig. 10.—Gallop rhythm in a case of arterial hypertension with congestive heart failure. Note the delay in the appearance of the sound that occurs at the beginning of ventricular systole (*1°*) and the anticipation of the auricular sound (*as*) as may be shown by the electrocardiogram, simultaneously obtained.

at the end of the diastolic pause (presystolic gallop rhythm) will be found at its beginning (protodiastolic gallop rhythm) (Laubry and Pezzi,¹⁸ White,¹⁰ Cossio⁶) (Figs. 7 and 8).

The delayed appearance of the sound that is produced at the beginning of the ventricular systole, which is due not to delayed auriculo-ventricular conduction but to a disturbance in the intraventricular conduction, or is caused by a deficiency of the ventricular muscle, produces the separation of the auricular sound from the sound that appears at the initiation of the ventricular systole. This separation also results in the appearance of two successive sounds instead of a single first heart sound (Figs. 9 and 10).

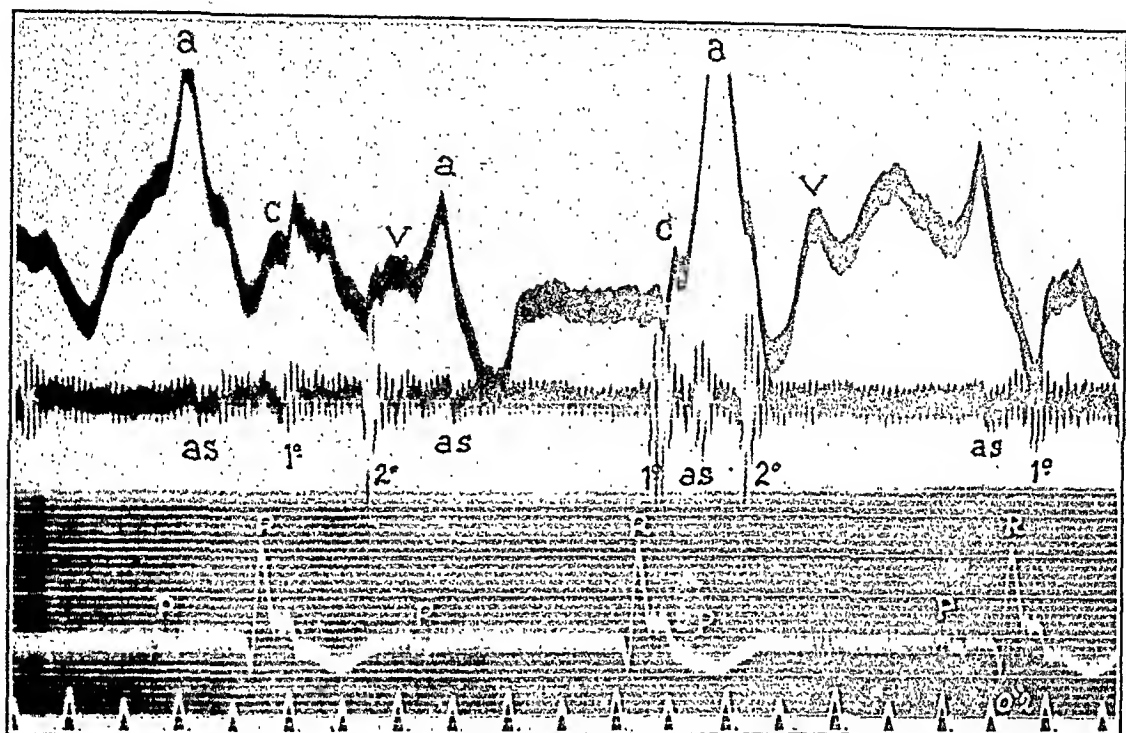


Fig. 11.—Venous pulse, electrocardiogram, and graphic record of the heart sounds in a case of complete heart-block. Note the increased intensity of the auricular sound (*as*) when the contraction of the auricles occurs during the ventricular systole.

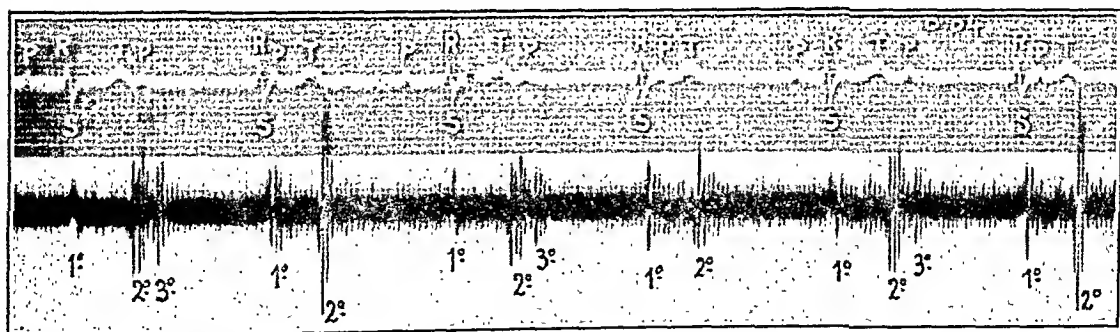


Fig. 12.—Electrocardiogram and graphic record of the heart sounds in a case of complete heart-block. Note the appearance of a third sound (3°) just after the second heart sound (2°), whenever the contraction of the auricles occurs after the ventricular contraction has come to an end, i.e., in the period of rapid filling.

The presence of these two successive sounds, the first auricular and the second ventricular, is known by the name of reduplication of the first heart sound or of presystolic gallop rhythm, according to the cadence. They occur in intraventricular heart-block, especially in the so-called bundle-branch block (Lewis,²⁰ Cossio⁶) and in heart failure

(Routier and Van Bogaert,²¹ Duchosal²²). In the latter condition it generally assumes the cadence of presystolic gallop rhythm on account of the coexistence of tachycardia and of the conspicuous separation between the auricular sound and the sound that exists at the beginning of ventricular systole. This conspicuous separation between both sounds is due to the fact that, besides the delay of the sound that appears at the beginning of the ventricular systole, there is an anticipation of the auricular sound in relation to the contraction of the auricles (Duchosal²²).

Complete Heart-Block.—The isolated contraction of the auricles in complete heart-block, i.e., when auricular contraction is not followed by the contraction of the ventricles, causes the auricular sound to appear as an individual phenomenon at the precordium. The complete independence of auricular and ventricular contraction in complete heart-block causes the auricular sound to appear at different moments during the heart's cycle, coinciding occasionally with the sound that is produced at the start of ventricular systole and also now and then with the period of ventricular rapid filling (Figs. 11 and 12). When the auricular sound appears during the great silence of diastole, we have to deal with a very muffled sound, at the extreme limit of audibility. When it appears in the short systolic silence, it is stronger (Cossio and Braun Menendez⁷) and may simulate a reduplication of the first or the second heart sound, according to its position. When the auricular sound coincides by chance with the sound that appears at the beginning of the ventricular systole, both acoustic phenomena are added, and in this case the first sound acquires unusual intensity and may be compared to a cannon shot (Strazhesko²⁴). When the auricular sound coincides occasionally with the period of rapid filling, which directly follows ventricular contraction, both effects are added, and there appears a third sound after the second sound of that heart cycle (Cossio and Lascalea²⁵).

SUMMARY

1. The auricular contraction produces a sound called auricular sound. The first part of that sound appears at the height of the auricular systole and is more evident at the esophagus. The second part of this sound occurs once the auricular systole is ended and is more evident at the precordium.
2. Under normal conditions the auricular sound is a part of the first heart sound but may appear as an independent sound, being the cause of most of the cases of reduplication of the first heart sound heard in healthy subjects.
3. In a series of abnormal conditions such as arterial hypertension, aortic incompetence, mitral stenosis, delay in the auriculoventricular conduction, and marked intraventricular block (the so-called bundle-branch block), the auricular sound may appear isolated, being the cause

of the acoustic phenomenon called reduplicated first sound and presystolic gallop rhythm that may be present under those circumstances.

4. In complete heart-block the auricular sound is also independent of ventricular systole and may appear during the great diastolic silence or the shorter systolic silence, simulating in this case a reduplication of the first or the second heart sound. It may likewise coincide and strengthen occasionally the first heart sound, or, if coinciding with the period of rapid filling of a heart cycle, cause the presence of a third heart sound following the second sound.

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ELECTROCARDIOGRAPHIC CHANGES FOLLOWING CORONARY SINUS OCCLUSION IN THE DOG'S HEART*†

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BASED upon observations made by Gross¹ on the available mechanisms by which the human heart attempts to compensate for occlusion of the coronary arteries or their branches, Gross and Blum^{2, 3, 4} produced obturation of the coronary sinus in the dog's heart in order to increase the vascular bed. They were able to show that, following coronary sinus obturation, ligation of the left anterior descending coronary branch either completely prevented the formation of an infarct, which otherwise almost invariably follows this procedure, or diminished its size considerably. The present report deals with the electrocardiographic findings in a series of 66 dogs on which partial or complete obturation of the mouth of the coronary sinus was produced.

Very few reports have been published on the effects of coronary sinus obturation. Cohnheim and von Schultess-Rechberg (1881)⁵ observed enormous stasis in the dog's myocardium following coronary sinus occlusion. Robertson⁶ observed bulging of the coronary sinus and veins, cyanosis of the left heart, petechial spots, slowing of the heart rate, and

TABLE I
METHODS EMPLOYED TO PRODUCE CORONARY SINUS OBTURATION AND
DEGREE OF OCCLUSION OBTAINED

PROCEDURE	NO. OF DOGS	DEGREE OF OCCLUSION		
		COMPLETE	PARTIAL	UNSUC- CESSFUL
I. Ligature alone	24	11	7	6
II. Ligature and dissection	5	5	0	0
III. Ligature and escharotics* (perisinus and intrasinus)	12	5	4	3
IV. Perisinus injection of escharotics	15	0	13	2
V. Intrasinus injection of escharotics by use of transauricular cannula	8	2	2	4
VI. Intrasinus injection of escharotics with temporary ligature†	2	2	0	0
Total	66	25	26	15

*Escharotics used were: 5 per cent and 10 per cent sodium morrhuate; 30 per cent sodium salicylate; tincture of green soap (1 to 2 c.c. were injected).

†Ligature around mouth of coronary sinus held in place from 5 to 10 minutes—then removed.

*From the Laboratories of The Mount Sinai Hospital.

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decreased contractility following such occlusion. The only report on electrocardiographic findings following coronary sinus occlusion is that by Otto.⁷ Although he also produced vagus nerve section in all of his twelve dogs, and section of the accelerator nerve in seven of them, he did not believe that this influenced the effects which he observed following coronary sinus ligation. Following this procedure, there occurred engorgement of the large veins, cyanosis, and functionless involvement of the left ventricle, incomplete heart-block and maintenance of the regular rhythm by the auricles. Ten of his twelve dogs died within an

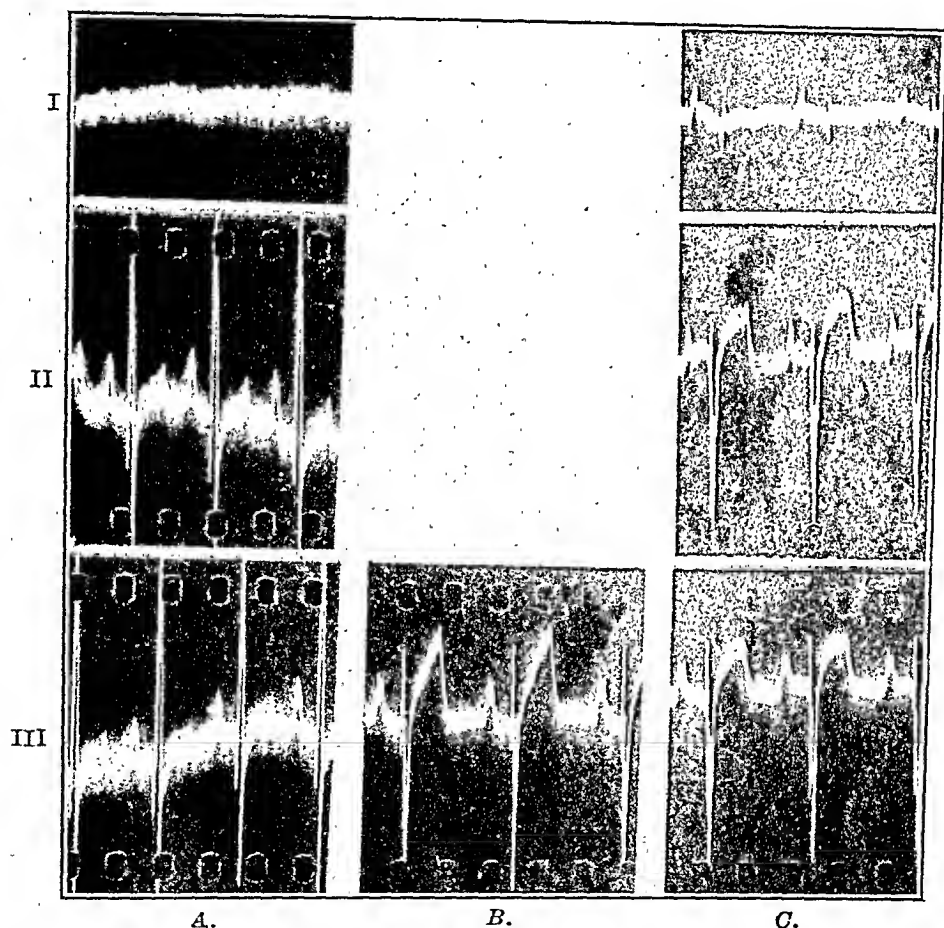


Fig. 1.—A, electrocardiogram taken under anesthesia before ligation of the coronary sinus. Note low voltage in Lead I.

B, Lead III taken seven minutes postoperatively. Note slowing of the heart, notching and downward direction of the QRS main deflection, and elevation of the R-T transition.

C, electrocardiogram taken twenty minutes postoperatively. Note the slowing of the heart, notching and downward direction of the QRS main deflection, and elevation of the R-T transition in Leads II and III.

hour following the coronary sinus occlusion. Electrocardiographic tracings (Lead II) showed constant elevation of the T-wave. In two instances R-T fusion appeared.

In the studies presently reported (incorporated in a preliminary report⁸), ligation and injection of escharotics (sodium morrhuate, sodium salicylate, and tincture of green soap) into and around the coronary sinus was employed to produce coronary sinus occlusion in sixty-six

dogs. All procedures were carried out as close to the coronary sinus mouth as possible. Complete, partial and unsuccessful obturations were obtained. Table I shows the methods employed and the degree of obturation obtained as determined at autopsy.

Electrocardiographic tracings were taken before, during, and at various intervals of time after the coronary sinus procedures. Because of the fact that low voltage frequently occurs in Lead I of dogs (Fig. 1), changes in this lead were difficult to evaluate and therefore were eliminated. The consistent electrocardiographic changes observed in the several groups of experiments were as follows: (1) elevation of the R-T transition; (2) notching and downward direction of the main QRS deflection; (3) inversion of the T-wave; and (4) temporary slowing of the heart rate.

Large T-waves of a transitory nature were occasionally noted. These were observed after the first week and occurred with equal frequency in the several groups of procedures listed. Partial heart-block was noted in two dogs in which the coronary sinus was completely ligated. Both of these dogs died within twenty-four hours after the operation.

Slowing of the heart rate was observed immediately following coronary sinus ligation. This occurred almost invariably. The slowing lasted a few minutes and did not take place when escharotics alone were used for the obturation. This was probably due to the fact that escharotics do not produce a sudden and complete obturation. It also indicates that the slowing of the heart rate following obturation is not due to irritation at the mouth of the coronary sinus.

Complete ligation of the coronary sinus produced a dilatation of the entire heart. The superficial veins became engorged and the left ven-

TABLE II
ELECTROCARDIOGRAPHIC FINDINGS FOLLOWING COMPLETE OBTURATION
OF CORONARY SINUS

PROCEDURE	DOGS WITH RECORDS IMMED. TO 24 HR.	DOGS WITH RECORDS 1 DAY TO 4 WK.	QRS		R-T	T
			DOWN	NOTCHED	ELEVA- TION	INVER- SION
I. Ligature alone	4	8	4 1	3 1	4 4	0 2
II. Ligature and dissection	4	5	0 0	2 1	4 5	4 4
III. Ligature and escharotics (perisinus and intra- sinus)	3	3	3 0	1 1	3 1	0 0
V. Intrasinus injection of escharotics by use of transauricular cannula	2	1	0 0	1 1	0* 0	0 0
VI. Intrasinus injection of escharotics with tem- porary ligature	2	1	0 0	0 0	1 0	1 0

*Temporary elevation of R-T while cannula was in place.

tricle became cyanotic up to and slightly beyond the interventricular grooves. Occasionally ecchymotic spots appeared on the surface of the left ventricle. The right ventricle retained its normal color except for a strip adjacent to the interventricular grooves, particularly on the posterior aspect of the heart.

Table II summarizes the electrocardiographic findings following complete obturation at the mouth of the coronary sinus.

As will be noted, all records taken immediately after complete ligation of the coronary sinus mouth, without dissection, showed a downward direction of the main deflection of the QRS and an elevation in the R-T transition (Fig. 2). Three of the four animals showed notching of

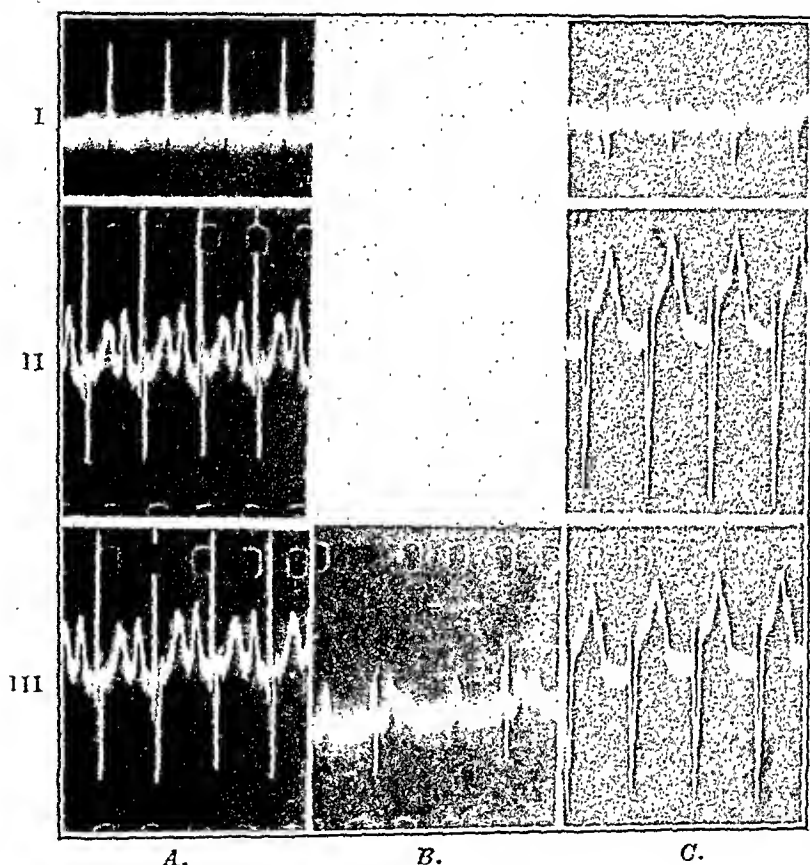


Fig. 2.—A, electrocardiogram taken under anesthesia before ligation of the coronary sinus.

B, Lead III taken fifteen minutes postoperatively showing 2 to 1 heart-block.

C, electrocardiogram taken thirty minutes postoperatively. Note the notching and downward direction of the QRS main deflection in all leads, and the elevation of the R-T transition in Leads II and III.

the QRS. When the coronary sinus was dissected before ligation, immediate records showed no downward direction of the QRS deflection; notching of the QRS was less frequent; the T-waves were inverted in all four cases; and the R-T transition was elevated (Fig. 3).

The combined procedure in which ligation and injection of escharotics either into or around the coronary sinus produced complete obturation, gave electrocardiographic results similar to those mentioned above; all cases showed elevation of the R-T transition and downward direction of the QRS deflection.

When complete obturation was obtained by thrombosis following injection of an escharotic into the lumen of the coronary sinus at its mouth, the electrocardiographic changes were inconstant. In one case (Table II) after the cannula was placed in the coronary sinus and the escharotic was introduced, the electrocardiogram showed an elevation of the R-T transition. After the cannula was removed the R-T elevation disappeared. This suggests that the R-T elevation may be related to the sudden increase in venous blood within the myocardium (anoxemia?).

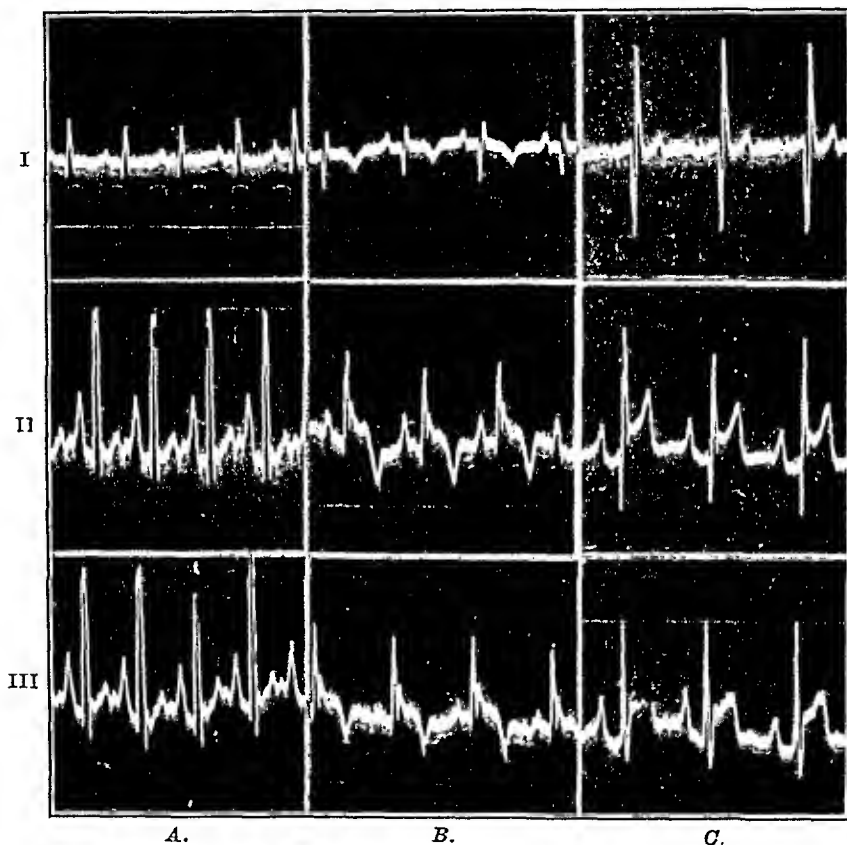


Fig. 3.—A, electrocardiogram taken under anesthesia before dissection and ligation of the coronary sinus.

B, electrocardiogram taken sixteen hours postoperatively. Note lower voltage, notching and slurring of the QRS, the elevation of the R-T transition in Leads II and III, and the deeply inverted T-waves in all leads.

C, electrocardiogram taken six days postoperatively. Note the persistence of the R-T transition elevation in Leads II and III and the return of the T-waves to the upright position.

All electrocardiographic changes tended to return to normal within from two to four weeks after obturation of the coronary sinus. The inconstancy of the electrocardiographic changes found in Groups V and VI where escharotics alone were used is probably due to the fact that occlusion was not immediate.

Partial occlusion of the coronary sinus was obtained in twenty-six dogs. Table III shows the procedures employed and the results obtained.

TABLE III
ELECTROCARDIOGRAPHIC FINDINGS FOLLOWING PARTIAL OBTURATION
OF CORONARY SINUS

PROCEDURE	DOGS WITH RECORDS IMMED. TO 1 DAY	DOGS WITH RECORDS 1 DAY TO 1 WK.	QRS		R-T	T
			DOWN	NOTCHED	ELEVA- TION	INVER- SION
I. Ligature alone	2	7	1 2	2 3	2 3	1 1
III. Ligature and escharotics (perisinus and intra- sinus)	3	3	1 0	1 0	2 0	1 1
IV. Perisinus injection of escharotics	11	10	0 0	0 2	7 7	7 3
V. Intrasinus injection of escharotics by use of transauricular cannula	2	1	0 0	1 1	1 1	0 0

As will be observed, both dogs in which ligation alone was performed showed immediate elevation of the R-T transition and notching of the QRS, one with an inverted T-wave and one with a downward direction of the QRS deflection. These changes occurred in spite of the fact that occlusion was only partial. The inconstancy of the other findings noted in Table III may be due to the differences in degree, time, and rate in which the partial occlusion, with its resulting venous stasis, occurred.

TABLE IV
ELECTROCARDIOGRAPHIC FINDINGS FOLLOWING UNSUCCESSFUL OBTURATION
OF CORONARY SINUS

PROCEDURE	DOGS WITH RECORDS IMMED. TO 1 DAY	DOGS WITH RECORDS 1 DAY TO 1 WK.	QRS		R-T	T
			DOWN	NOTCHED	ELEVA- TION	INVER- SION
I. Ligature alone	2	6	0 0	0 0	0 0	0 0
III. Ligature and escharotics (perisinus and intra- sinus)	1	3	0 0	0 1	0 1	0 0
IV. Perisinus injection of escharotics	1	1	0 0	0 1	0 1	0 0
V. Intrasinus injection of escharotics by use of transauricular cannula	4	2	2 1	3 1	3 1	1 0

Table IV shows the findings in fifteen dogs in which the several procedures listed failed to produce any narrowing of the mouth of the coronary sinus as determined at autopsy. The findings are of interest inasmuch as they form a control group to determine the effect of the several procedures alone without any appreciable coronary sinus occlusion and its effects on venous stasis within the myocardium. It will be

observed that, when a ligature was placed around the coronary sinus and no injection of escharotics was employed, the electrocardiographic findings were completely negative. On the other hand, when escharotics were also used, electrocardiographic changes were sometimes present. In this latter group, it is quite possible that the injection of an escharotic may have produced some degree of obturation (mechanically, by infiltration) which, however, had completely disappeared when the dogs came to autopsy.

It is clear from the above described findings that when ligation alone was employed and occlusion was complete, electrocardiographic changes occurred in all instances; when ligation alone was employed and the lumen of the coronary sinus was not narrowed due to the fact that either accidentally or deliberately the ligature was not tied around the coronary sinus mouth, no electrocardiographic changes followed. Between these two clear-cut groups there are a number of instances in which at some time during the course of the experiment, and not immediately after the experimental procedure, partial or complete occlusion of the coronary sinus mouth was produced. In these groups the electrocardiographic findings were inconstant, but when present were of the nature of those described above.

SUMMARY AND CONCLUSIONS

Partial and complete obturation of the mouth of the coronary sinus was produced in forty-one dogs by means of a variety of procedures including ligation and the injection of escharotics into the coronary sinus lumen or around the coronary sinus. These procedures were employed alone or in combinations. In fifteen additional dogs these procedures were employed without producing appreciable coronary sinus obturation, as determined at autopsy.

Following complete obturation, there occurred dilatation of the heart, engorgement of the superficial veins, and cyanosis of the left ventricle up to and slightly beyond the interventricular grooves. Occasionally small ecchymoses were also observed. The electrocardiographic findings resulting from complete or partial occlusion were notching and downward direction of the main QRS deflection, elevation of the R-T transition, occasional inversion of the T-waves, and temporary slowing of the heart rate. These findings were most constant when occlusion was complete and sudden. It may be of interest to note that the inversion of the T-wave occurred almost invariably if the complete obturation was preceded by dissection of the coronary sinus. This brings up the question as to what rôle this additional injury may have played in the production of the electrocardiographic changes. On the other hand, the marked RST changes occurred whether or not there was local injury to the heart. These were, therefore, probably associated with congestion of the heart.

A contributing factor in causing inversion of the QRS deflection may have been the change in position or rotation of the heart produced by the congestion which occurred mainly in the left chambers.

No changes were found following the insertion of the ligature around the coronary sinus without occlusion. Partial obturation produced electrocardiographic findings similar to complete occlusion, but the changes were less constant in their occurrence. All electrocardiographic changes tended to disappear within a period of from two to four weeks after the occlusion was produced.

The RST changes, when present, were similar to those observed following acute coronary occlusion, but unlike the latter they did not present the pathognomonic steady progression into inverted T-waves. Thus, following coronary sinus occlusion, the heart gradually readjusts itself, and the electrocardiographic tracings return to normal.

It is suggested that the electrocardiographic findings reported may result from a temporary injury of the myocardium due to oxygen insufficiency attendant on venous congestion. Other factors, such as local injury due to manipulation, and change in the position of the heart, probably play minor rôles.

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DIGITALIS EOSINOPHILIA*

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RECENT observation of a patient who manifested an eosinophilia, seemingly in response to digitalis ingestion, led to a review of the literature on this subject. While some clinicians of wide experience appear to have encountered an occasional case, only two published authentic descriptions of this association could be discovered. The earliest such report that came to our notice was that of Recht¹ who observed in two patients that an eosinophilia of from 12 to 18 per cent could repeatedly be induced by the administration of digitalis leaf. More recently Smith and Benner² reported in detail a patient in whom recurrences of eosinophilia reaching 30 per cent coincided with successive periods of digitalization.

We believe the following case is an instance of eosinophilia due to digitalis:

CASE REPORT

W. E. M., a white, retired clergyman, aged seventy years, was admitted to the Psychiatric Clinic of the New Haven Hospital on Sept. 12, 1934, because of organic confusion and disorientation.

The family history, as well as the patient's past history, was negative for parasitic infestation, skin diseases, allergic manifestations, migraine, and the convulsive state. Repeated blood examinations of the patient's two children, in consideration of a possible familial eosinophilia, disclosed normal eosinophile counts.

At the age of twenty-eight years the patient developed an acute articular rheumatism which incapacitated him for six months. When he was fifty-five years old, during a short hospital admission for dental surgery, a late systolic murmur was heard at the cardiac apex and was believed to indicate disease of the mitral valve. One year later he returned with cardiorespiratory symptoms, and at this time he presented frank signs of mitral stenosis and insufficiency, with paroxysmal tachycardia, right hydrothorax, and either pneumonia or infarction in the right lung. Under a regime of rest and digitalis therapy good cardiac compensation was regained, and the patient was discharged. A single blood count, which had been done on admission, revealed 2 per cent of eosinophiles.

During the next ten years, from 1920 to 1930, fair cardiac compensation was maintained on 1 gm. of digitalis leaf per week. He was seen twice at intervals of five years because of exacerbations of cardiac symptoms, and on each of these occasions auricular fibrillation was noted clinically and confirmed by the electrocardiogram. Five years before admission the patient suffered arterial embolism in the right foot, followed by pneumonia and herpes zoster. He was treated at home and recovered uneventfully. Except for occasional brief spells of epigastric distress associated with dyspnea and tachycardia, the cardiac course continued satisfactorily on the usual maintenance doses of digitalis.

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During the last decade the patient was subject to brief syncopal attacks unassociated with convulsions, but occasionally followed by temporary confusion and amnesia. Mentally he evidenced a progressive, irreversible organic mental deterioration characterized by irritability, suspicion, fluctuations of the level of consciousness, and defects of memory for recent events. He was finally admitted to the hospital because of the custodial problem he presented.

Physical Examination.—The patient was a well-developed, senile white male in good nutritive state. He was neither dyspneic nor orthopneic; the neck veins were not engorged; and the lips were of good color. There was no edema of the eyelids. The eyegrounds revealed sclerosis of the vessels commensurate with his age; there were no retinal hemorrhages, scars, or exudate. Moderate cardiac enlargement was apparent from the position of the apex impulse in the fifth left intercostal space at the anterior axillary line. The heart sounds were regular, of good quality, and exhibited the typical auscultatory signs of mitral stenosis and insufficiency. Although the right radial pulse was definitely smaller in volume than the left (? old embolus), the blood pressure in each arm was 160 systolic and 90 diastolic. The chest was normal in conformation and mobility, and it yielded a generally resonant note on percussion. The expiratory murmur was slightly prolonged, and a moderate number of medium and coarse crepitant râles were heard over both lower lobes; no musical râles were audible. The liver edge was barely palpable. There was no edema of the extremities or over the sacrum. The skin was loose and inelastic and free from eruption. No muscle tenderness could be elicited. The temperature, pulse, and respirations were normal.

Laboratory Findings on admission revealed a red cell count of 4,790,000 with 107 per cent hemoglobin (Sahli), and a leucocytosis of 12,950 cells per cubic millimeter, of which 22 per cent were eosinophiles. There was a transient albuminuria. The blood Kahn and Wassermann tests were negative. The sputum revealed no acid-fast bacilli, elastic fibers, or Curschmann's spirals; not more than 2 eosinophiles per field were seen with the high power objective. Repeated stool examinations, by concentration methods, were negative for parasites, ova, and blood. Intracutaneous tests with trichiniasis antigen in dilutions of 1:10,000 and 1:500 were negative. The electrocardiogram on Oct. 1, 1934, when the patient was theoretically overdigitalized, revealed only a sino-auricular tachycardia, with a left axis deviation. Another tracing six weeks later, when the patient had theoretically been adequately redigitalized, showed normal and upright T-waves in all leads, and only a very slight depression of the S-T segment in Lead I; the P-R intervals, which had previously been 0.20 sec. in duration, now measured 0.21 sec.

Course in Hospital.—Three days after admission the patient became febrile, and during the next two weeks he ran the typical course of a mild bronchopneumonia. Thereafter he was ambulatory and was without significant cardiorespiratory symptoms practically throughout his three months of hospitalization. However, he did exhibit a persistent, slight expiratory dyspnea together with an occasional moderate afternoon fever. The pulse level varied between 100 and 120 per minute. Because of the persistence of tachycardia and slight basal pulmonary congestion, the maintenance digitalis dosage was cautiously increased from 10 c.c. of the tincture per week to 21 c.c. per week. Although a total of 48 c.c. of the drug was administered during the following sixteen days, there ensued no clinical improvement, change in the pulse, or digitalis intoxication. An electrocardiogram taken toward the end of this period (October 1) gave no evidence of digitalis effect. Throughout this period, both before and during the administration of the excess digitalis, the white cell count remained elevated at 12,000 to 15,000, and the eosinophiles maintained a level around 20 per cent.

Believing that the usual causes for eosinophilia had been excluded and suspecting that digitalis was an etiological factor, we deliberately withheld the drug for

twenty-two days. During this interval the patient's clinical course continued unchanged, but the decline of the eosinophiles to normal levels, as depicted in Fig. 1, was striking. On the resumption of digitalis medication, a new supply of fresh tincture was used, and the eosinophiles again rose rapidly to their previous high level. Although digitalis was again given in unusually large doses (16 c.c. in two days, followed by 3 c.c. daily for seven weeks), there were, as before, no frank clinical or electrocardiographic evidences of digitalis effect. (This same digitalis tincture appeared adequately potent when administered in the usual doses to other patients with congestive failure.)

The mental status was one of apprehension, paranoid delusions, and fluctuating disorientation. The patient was often noisy during the night, and an occasional sedative of 0.6 gm. of barbital was administered. On the night of December 11 he was more disturbing than usual, and the barbital sedative was given twice. The following morning he was stuporous; the pupils were dilated; and the superficial abdominal and deep tendon reflexes were sluggish. During the day the pulse and temperature rose, the breathing became stertorous, and signs of bronchopneumonia appeared. He continued in this state until his death four days later.

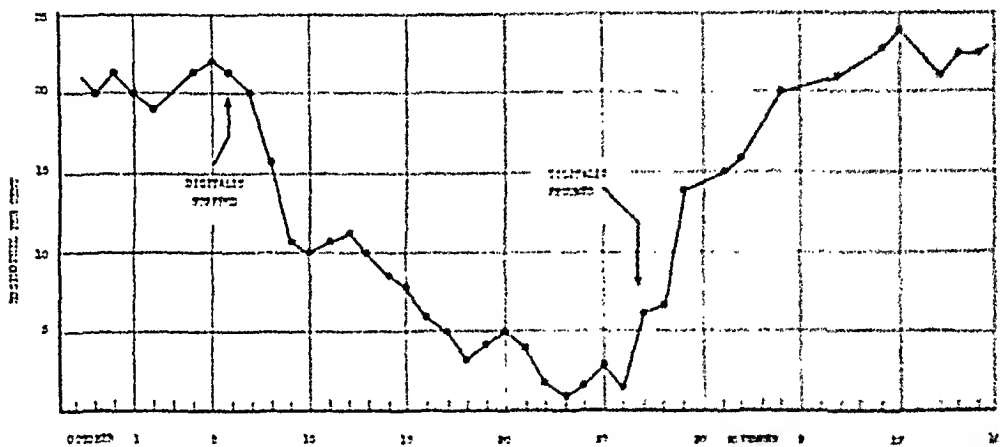


Fig. 1.—Relation of eosinophilia to digitalis medication. Eosinophilia for preceding two weeks averaged 17 per cent and for the succeeding month, 25 per cent.

Necropsy was performed by Dr. Gustave Freeman. The heart with the pericardium weighed 685 gm. and showed moderate hypertrophy of the right auricle and ventricle. An organized mural thrombus occupied the greater part of the left auricle. In addition to stenosis of the mitral valve, there was arteriosclerotic narrowing of the aortic orifice. Microscopically no typical Aschoff bodies were seen. Atheromatous plaques were found in the coronary vessels, and the muscular coats of these vessels here and there harbored groups of small mononuclear cells with bizarre outlines and basophilic cytoplasm.

The lungs felt doughy, the lower lobes were firm, and patches of thickened pleura covered both posterolateral surfaces. The bronchi contained a yellow, purulent material which covered the dark, velvety mucosal lining. Microscopically one could see in the thickened pleura an exudative process with plasma cells and an occasional binucleated giant cell. The pulmonary parenchyma was involved in a fibrosis which was pronounced in several areas; in these regions the enclosed, separated alveoli were lined with cuboidal or columnar epithelial cells. These lesions, which simulated a bronchiolar fibro-adenoma, usually occurred in the vicinity of dilated bronchioles containing purulent exudate and occasionally desquamated epithelial linings. Throughout, one saw focal areas of necrosis with polymorphonuclear exudate. The material which filled the bronchi was peculiar in that the cellu-

lar débris was often arranged in layers of columns which conformed to the longitudinal direction of the tube. A moderate amount of peribronchial muscular hypertrophy was evident. Besides the acute inflammatory process, large numbers of "heart failure cells" abounded. Many of the groups of phagocytes contained large fat vacuoles. The vascular walls were thick and the lumina often diminished.

Both renal surfaces were finely granular, and the capsules were adherent. Hyalinized glomeruli were found in areas of interstitial fibrosis. The liver showed the changes of chronic passive congestion around the central veins. In the brain there was a slight degree of cortical atrophy which was most evident in the frontal lobes. Microscopically, senile plaques and advanced atheromatous changes in the vessels were the only noteworthy changes.

Sections of the deltoid and gastrocnemius muscles gave no evidence of parasites, fibrosis, or inflammation. The other viscera were not remarkable.

DISCUSSION

We believe that the usual causes of eosinophilia have been excluded as factors in the case here presented and that digitalis played an important etiological rôle in the blood dyscrasia. While an eosinophilia associated with, and apparently influenced by, digitalis is in itself a noteworthy phenomenon, even more interesting is the speculation that is aroused as to the nature and mechanism of this response.

Vagotonia appears to be a popular current theory in explanation of some forms of eosinophilia (Schilling³). Bertelli, Falta, and Schweeger,⁴ first observed that a moderate eosinophilia often followed the injection of pilocarpine, while a diminution in the number of these cells occurred after atropine. Eppinger and Hess,⁵ in their monograph on vagotonia, repeatedly mention eosinophilia as a manifestation of this syndrome. More recently Hajós and his collaborators⁷ have reported a moderate rise in eosinophilic cells in eight out of ten rabbits during prolonged faradic stimulation of the cut vagi; the responses were small, however, and the observations were not reported in sufficient detail to carry complete conviction. Chillingworth and his collaborators⁶ noted a definite eosinophilic cell increase lasting several days in dogs in which partial obstruction to expiration was produced by an intratracheal ball-valve mechanism. They also studied fifteen normal human beings and detected an immediate, slight but definite rise in eosinophiles apparently produced by the resistance to expiration offered by a partially blocked flutter valve through which the subjects breathed for only a few minutes. These observations were regarded as evidence of a vagotonic basis for eosinophilia, and the mechanism was explained with the theory that the initiating factor was an overdistention of the alveoli which, through vagus stimulation, ultimately brought about a release of eosinophiles from blood-forming organs or blood reservoirs. Furthermore, the authors offered in their experiments an explanation to replace the older "blood acidity" theory of eosinophilia. Pescatori⁸ was the first to state the belief that the increased carbon dioxide content of the blood in the "partial asphyxia" of asthma and emphysema constituted

a specific stimulus for eosinophile production. Banerji's experiments are sometimes cited in substantiation of this theory, but the very slight eosinophilic cell increases he observed in a few rabbits which were subjected to asphyxia were not at all convincing. Chillingworth and his associates argue that it was not the increased blood carbon dioxide resulting from respiratory obstruction, but rather the associated alveolar distention which constituted the important eosinophile-stimulating fac-

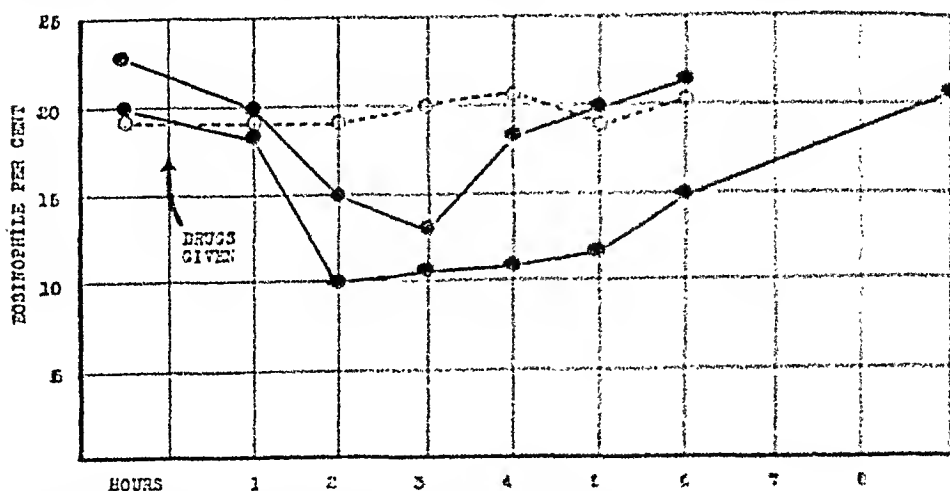


Fig. 2.—Effect of atropine and pilocarpine on eosinophilia.
 ●—● Atropine sulphate (0.2 mg.) injected on two occasions.
 ○—○ Pilocarpine hydrochloride (0.5 mg.).

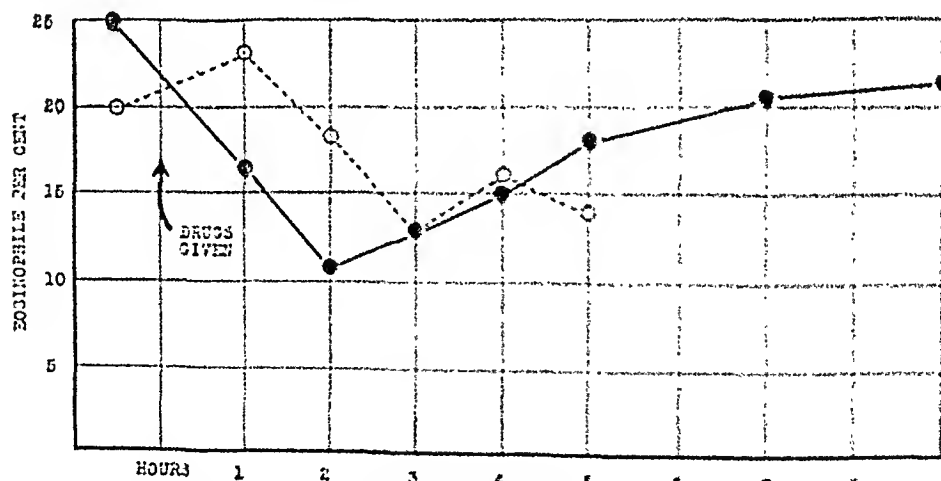


Fig. 3.—The effect of epinephrine on eosinophilia. Injected epinephrine hydrochloride (1:1000 dilution):

○—○ Effect of 0.5 c.c.
 ●—● Effect of 0.75 c.c.

tor. In corroboration they state their observation that in uncomplicated emphysema no eosinophilia is observed in spite of the elevated carbon dioxide tension which prevails in this condition.

Consistent with the vagotonic theory of eosinophilia would be the diminution in number of these cells caused by either adrenalin or atropine, and their increase by pilocarpine or choline esters. Such

effects with pilocarpine and adrenalin were observed by Wieck⁹ in a patient with vagotomie manifestations who exhibited a persistent but obscure eosinophilia. Our patient was injected on different days with 0.5 mg. pilocarpine hydrochloride, twice with 0.9 mg. atropine sulphate, and on two occasions with adrenalin hydrochloride solution. Although no unusual reactions occurred with any of these drugs, the depression of the eosinophile level by both adrenalin and atropine seemed definite, while with pilocarpine there was no apparent effect (Figs. 2, 3). Unfortunately, a choline preparation was not available in time for trial. Smith and Benner² likewise noted a fall in eosinophile percentage after therapeutic doses of adrenalin and atropine, but no change following pilocarpine.

Although it is inviting to invoke the vagal effects of digitalis in explanation of the eosinophilia in our case, it is noteworthy that the patient appeared actually refractory to the drug. The rate and character of the pulse were not influenced by excessive doses of the drug; the electrocardiographic films indicated no digitalis effect even after presumably toxic doses had been given; and there was no decline in the patient's clinical state during the three-week period when digitalis was entirely withheld. That digitalis, rather than pulmonary pathology, was the principal etiological factor in the eosinophilia would seem probable in view of the striking alterations in the level of these cells coincidental with digitalis administration and withdrawal.

SUMMARY

A case of eosinophilia presumably due to digitalis is described, and the alleged vagotomie mechanism of the blood response is discussed.

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FUNCTIONAL CAPACITY OF THE NORMAL PERICARDIUM

AN EXPERIMENTAL STUDY*

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IN THE normal animal the limits to which the heart can rapidly dilate are fixed by the capacity of the pericardial sac; since Barnard¹ in 1897 showed experimentally that the pericardium is a practically inelastic structure and its capacity is therefore relatively fixed as far as acute distention is concerned. Accordingly, the question arises as to what extent the pericardium normally restricts the ability of the heart to dilate and, from the clinical standpoint, whether it is worth tapping relatively small pericardial effusions when they occur within a short space of time, e.g., as a result of trauma. In this connection it must be emphasized that this study concerns itself only with rapidly accumulating effusions as best exemplified by trauma and not those occurring more slowly as the result of inflammatory process where large effusions can occur (e.g., 1,500 to 2,000 c.c. or more). This entire subject has been studied from a number of angles, but the conclusions have not been entirely concordant (see review by Wiggers¹⁷ in 1929).

Barnard¹ in 1897 showed that at constant high venous pressures removal of the pericardium increased the filling of the ventricles to a marked extent, and similar observations were made by L. Hill² and by Evans and Matsuoka.⁴ Kuno⁹ in 1917 using heart-lung preparations found that even from 3 to 5 c.c. of fluid introduced into the pericardial sac of the dog caused an increase in the venous pressure and a decrease in the output of the left ventricle, and he concluded that the pericardium exercises, under every condition of venous inflow, a certain amount of resistance to diastolic expansion of the heart.

Van Liere and Allen¹⁵ in 1927 and Van Liere and Crisler¹⁶ in 1930 concluded from their experiments on acute cardiac dilatation in dogs that the pericardium might have a protective action in conditions of extreme stress on the heart. Rossler and Unna¹³ in 1935 claimed that the pericardium in acutely damaged hearts prevents overdilatation of the right heart.

The mechanism of any restraining action which the pericardium might have was studied by Wilson and Meek¹⁸ in 1927. They found that the restraining influence of the pericardium was abolished when the pericardio-diaphragmatic attachments were cut and hence attributed any interference which the pericardium might exert on cardiac filling, not

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to a lack of space but to diaphragmatic pull drawing the upper lateral walls over the auricles and thereby reducing their filling. From their observations it seemed that the limits of pericardial capacity were reached in normal dogs when the effective venous pressure was increased to three times its normal value.

On the other side of this question, observations have been advanced to show that there is ample room for diastolic distention within the pericardium. Thus Henderson and Prince⁶ found by autopsy measurements in human beings that the average capacity of the pericardial sac (including the capacity of the heart itself) was from 3.5 to 5 c.c. per kilogram of body weight, and since the maximum stroke volume never exceeds 2 c.c. per kilogram, they concluded that a considerable margin was left for further dilatation.

Also it has been shown that removal of the pericardium produces no demonstrable effects. Mazzone¹⁰ in 1912 and Rehn¹² in 1913 studied dogs in which the pericardium had been removed and found no ill effects on the health of the animals. Beck and Moore² in 1925 removed the pericardium in five dogs and subjected them to severe exercise. They found that these animals responded very well to exercise. Furthermore, a number of clinical cases of partial or total congenital absence of the pericardium without producing any clinical symptoms have been reported.^{11, 5}

In order to determine the capacity of the pericardium, experimental injection of the normal human pericardial sac after death has been carried out. These experiments showed that from 150 to 200 c.c. of liquid completely filled the complementary spaces of the pericardium and distended the sac.³ However, this does not necessarily correspond to conditions in the living.

As far as actual measurement of the capacity of the pericardium of living animals is concerned, the reported observations are not very numerous. Starling¹⁴ in 1897 reported observations on one living dog in which he found that injection of 40 c.c. of oil into the pericardial sac caused a slight rise in venous pressure and that injection of 70 c.c. of oil caused in addition to a marked rise in venous pressure, a fall in arterial pressure. Katz and Gauchat⁸ in 1924 injected oil and also saline into the pericardial sacs of dogs in amounts up to 120 c.c., obtaining a rise in venous pressure, a fall in blood pressure, and a pulsus paradoxus; but they did not note the point at which the venous pressure first began to rise.

It was our purpose to carry these observations further by determining the amount of fluid that could be introduced into the pericardium of living dogs without interfering with the function of the heart in any way.

METHOD

The effective capacity of the pericardium was measured directly in twenty living dogs. This was done by allowing warm saline solution to run from a buret through a special cannula into the pericardial sac. The height of the venous pressure was meanwhile measured by means of a water manometer connected with a cannula inserted through the external jugular vein into the superior vena cava.

It has been demonstrated experimentally that a rise in venous pressure is the first effect produced by increasing the pressure in the pericardial sac. This is followed by diminished ventricular filling and a fall in blood pressure. By the method outlined above, we were able, therefore, to determine the maximum volume of warm saline that could be introduced into the closed pericardial sac without producing an impairment of cardiac filling.

Measurements were made on twenty dogs with normal venous pressures, shortly after complete barbital anesthesia and opening of the chest. The pericardio-diaphragmatic attachments were left intact. During the tests artificial respiration was so regulated that the dogs just failed to breathe naturally.

RESULTS

The results obtained are shown in Table I. The dogs' weights varied between 7.5 and 17.0 kg., the heart weights between 64 and 167.5 gm. and the amounts of warm saline that could be introduced without any interference to ventricular filling varied between 21 and 79 c.c. A study of these results shows at a glance that a general relationship exists be-

TABLE I

EXPER. NO.	WT. OF DOG IN KG.	WT. OF HEART IN GM.	CAPACITY OF PERICARDIUM IN C.C.	RATIO— HEART WT.: PERICARD. CAP.
1	10.2	89	30	3:1
2	11.75	120	33	3.6:1
3	7.5	67	21	3.2:1
4	15.75	145	56	2.6:1
5	12.5	70	30	2.3:1
6	--	90	29	3.1:1
7	14.0	105.5	75	1.4:1
8	16.5	162	79	2.1:1
9	13.5	115	40	2.9:1
10	8.5	64	42	1.5:1
11	9.5	93	44	2.1:1
12	14.5	177	45	3.9:1
13	15.0	108	27	4:1
14	17.0	152	44	3.5:1
15	12.25	140	48	2.9:1
16	12.0	108.5	39	2.8:1
17	13.5	117	48	2.4:1
18	10.5	115	32.5	3.6:1
19	15.5	167.5	44	3.8:1
20	11.5	77	34	2.3:1
Average—Heart Weight: Pericardial Capacity = 2.9:1				

tween heart weight and body weight on one hand and pericardial capacity on the other. Considerable variation in this ratio occurred, however, in different animals. This was to be expected in view of the different types of dogs used and their different antecedent histories (some of them probably had led very inactive lives while others might even have been used on the race track). The ratio of heart weight to pericardial capacity varied between 1.4:1 and 3.9:1, but the majority ranged around a 3:1 ratio. If these ratios are applicable to normal human hearts weighing 250 to 300 gm., then a pericardial capacity in human beings of about 80 to 100 c.c. can be inferred. This may be an indication of the size of rapidly accumulating effusions which might embarrass the heart.

Since the values obtained experimentally in dogs and those inferred for man are greater than the systolic discharge of the heart (which in man according to Grollman averages about 62 c.c.), the conclusion is justified that the pericardial sac offers an ample margin by which the normal heart may dilate.

SUMMARY

1. Measurements were made of the amount of saline which could be introduced into the pericardium of each of twenty living dogs before a rise in venous pressure occurred.

2. The amounts which could be introduced varied between 21 and 79 c.c.

3. The ratio of the heart weight to pericardial capacity varied between 1.4:1 and 3.9:1, but in the majority of instances was about 3:1.

4. Applying this ratio to normal human hearts a human pericardial capacity of about 80 to 100 c.c. can be inferred.

5. The pericardial sac offers an ample margin by which the normal heart may dilate.

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Department of Clinical Reports

ANOMALY OF THE RIGHT CORONARY ARTERY IN A YOUNG PATIENT WITH AORTIC VALVULAR DISEASE, CARDIAC ENLARGEMENT, AND ANGINA PECTORIS*

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ANOMALIES of the coronary arteries are sufficiently unusual to justify placing on record this case of duplication and stenosis of the right coronary artery with abnormal distribution of the vessels.

CASE REPORT

C. H., male, aged sixteen years, was admitted to the charity service of Baptist Memorial Hospital (28,896) Nov. 13, 1930, on the service of Dr. John Maury, Jr. He gave the history of an attack of rheumatic fever with heart involvement in 1924. About two and a half years before admission, while in bed with pleurisy, he had some palpitation. After six weeks in bed, he returned to school, but this effort caused palpitation and some dyspnea and precordial pain which gradually grew worse. He was examined and sent to a hospital in Kansas City.

In 1929 he began to have severe pain about his heart, that radiated down his arms. At the beginning these pains occurred weeks apart, but gradually they appeared more frequently, until on admission he was having from 3 to 5 attacks in twenty-four hours. The pain was very severe, lasting on the average about an hour, but in one instance lasting four hours. Morphine seemed to relieve the pain, and he had taken as much as 1 grain at a time to obtain comfort.

He also complained of rapid heart action, the shock of the heartbeat against the chest wall, and of swelling of the feet.

Physical examination revealed an anemic and undernourished boy, with a marked precordial bulge, pulsation, and shock. Visible pulsations were noted in the neck and abdomen. The heart was greatly enlarged, the apex beat being in the midaxilla, seventh interspace. Systolic and diastolic murmurs were heard over the heart, especially at the aortic area, and were transmitted to the neck. The rate was 100-120, rhythm regular. He had a water-hammer pulse. The blood pressure was 140/20 in the right arm, 80/10 in the left.

Laboratory tests at this time showed: red cell count, 3,960,000; hemoglobin (Sahli) 65 per cent; white cell count and differential count were normal. Urinalysis was negative; blood Wassermann, negative; and blood culture, negative (six days).

The electrocardiogram showed a heart rate of 100, with a normal rhythm. P₂ was notched; the QRS complex was widened (0.1-0.12 sec.), was upright, was slurred and notched in Lead I, upright and slurred in Lead II, and diphasic in Lead III. T₁ was inverted; T₂, diphasic; T₃, upright. My impression was that there was left ventricular preponderance with probable coronary obstruction.

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The teleroentgenogram gave these measurements: RM, 7 cm.; LM, 8.8 cm.; transverse, 15.8 cm.; length 18.5 cm.; transverse aorta, 8 cm.; internal thoracic diameter, 22.7 cm.

On December 13, Dr. R. Eustace Semmes attempted alcoholic injections of the paravertebral nerve areas, but because of a moderate scoliosis of the cervical spine, this was not successful. There were no areas of anesthesia present the next day, and no apparent relief of symptoms.

On December 15 the following was reported: "X-ray films of the cervical and dorsal spine showed some arthritic changes in the dorsal portion, not extensive, considerable curvature of the spine, with lordosis in the cervical area."

In January he suffered from a feverish "cold," during which the heart pain disappeared.

On January 26, 1931, Dr. Semmes operated on him and cut the sensory nerve roots under novocaine anesthesia. Laminectomy of last cervical and first two dorsal vertebrae was performed. The dura was opened, exposing the cord. When the nerve roots were stimulated, the patient identified the sensory roots of the last cervical and first three dorsal segments (and only these) as those conducting the pain. These roots were severed.

The operation was followed by extreme pain in the chest, probably due to a pericarditis, as evidenced by a friction rub.

For a week after the operation there was no angina. Four or five times a day, however, he suffered from a "heavy, smothering feeling" in the left chest. This was considered to be an anginal equivalent. There remained some sensation to touch and pressure over the left side of the chest, but less than on the right.

In early February he had mild bronchopneumonia.

About February 21 for a few nights he had anginal attacks over the heart and down the left arm. He thought there was some vague, unexplainable difference between these and the previous spells. There was not much numbness or alteration in sensation over the chest. At the sixth rib and below on the left there was distinct hyperesthesia. It was surprising there was not more sensory loss, but because of his severe illness and the frequent use of drugs, it was not certain that his full cooperation was obtained.

He was discharged to his home but reentered the hospital March 28 on the service of Dr. William C. Colbert. His condition got worse at home, and he had two or more severe anginal spells a day.

On April 6 he went into a coma and died.

Clinical Diagnosis.—Rheumatic heart disease, cardiac enlargement, aortic and mitral valvular disease, coronary sclerosis, angina pectoris, dilatation of aorta (ascending).

Autopsy was performed on April 6, 1931, by Dr. N. E. Leake and the author. The body was that of a white male, presenting evidence of emaciation and marked anemia. There was no edema. There was bulging of the precordium with a marked deformity of the chest framework. A linear scar over vertebral column extended from the lower cervical region downward about 4 inches.

Chest.—The bulging precordial area was due to an enormous heart, which weighed 740 gm. The relationship of this organ to the chest cavity was normal except for its size. The base of the heart extended well up into the upper portion of the right chest while the apex reached in the left lower chest to a level of the seventh rib in the anterior axillary line. No pericardial adhesions were present, but there was 160 c.c. of yellowish, amber, turbid fluid in the pericardial sac. The ascending portion of the aortic arch was somewhat dilated. The heart was removed and examined; the following findings resulted: The wall of the right ventricle was poorly developed and very thin, 5 mm. at the thickest part, 1.5 to 2

mm. at the thinnest. The tricuspid valve was normal. Right auricle was normal except for thin wall, and slight dilatation. The left ventricle showed marked hypertrophy and dilatation, the ventricular wall being 19 mm. thick. The aortic valve leaflets were thick but not adherent, but the thickness and stiffness caused some degree of aortic stenosis, and their retraction permitted considerable regurgitation. The mitral valve was slightly thickened in some portions and moderately so in others, and it was also retracted. There were no fresh vegetations on either valve. On the wall of the aorta, which was otherwise smooth and glistening, there were two slightly elevated, soft pinkish gray areas, translucent, about 1 cm. in diameter, suggestive of sessile vegetations. These did not involve the mouths of the coronary arteries.

The left coronary orifice measured 5 mm. in diameter. The coronary artery itself when opened measured 14 mm. in circumference. The wall was smooth, and there were no abnormalities as far as the vessels could be traced.

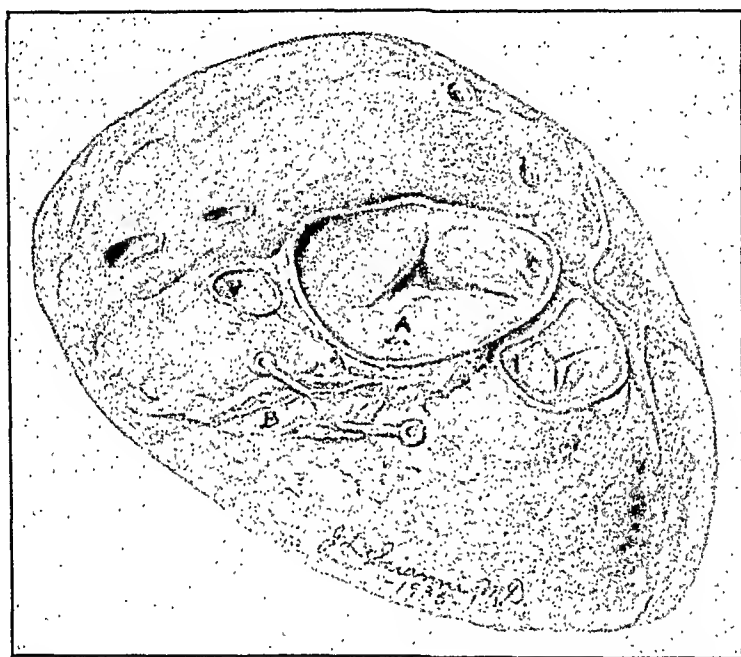


Fig. 1.—Drawing illustrating the anomalous openings of the right coronary artery (A), and the short vessel coming from the smaller opening (B). The thickening and retraction of the aortic cusps is also shown. The drawing was made from the fixed specimen by J. L. Scianni, M.D., of the Art Department, Division of Pathology, College of Medicine, University of Tennessee.

The orifice of the right coronary artery was double, the larger aperture measuring 2 mm. in diameter, the smaller about 0.75 mm. in diameter. (Fig. 1.) These apertures led into separate vessels that had no connection. The circumference of the larger of the two was 9.5 mm. The vessel was otherwise normal except for its distribution. The smaller aperture led into a fair sized vessel (record of measure lost) which after a course of an inch and a half plunged boldly into the musculature.

The lungs presented evidence of moderate chronic passive congestion at the inferior pole of the right lower lobe.

All abdominal viscera presented chronic passive congestion. No increase in intraperitoneal fluid was noted. The liver was greatly enlarged and unusually dark reddish blue in color. The spleen was enlarged, similar to the liver in color. No abdominal viscera were disturbed.

Anatomical Diagnosis.—Congenital malformation (duplication and stenosis of the right coronary orifice). Abnormal distribution of the right coronary vessels. Stenosis and regurgitation of the aortic valve, probably rheumatic in origin. Slight thickening of mitral valve (with insufficiency). Dilatation and hypertrophy of the left ventricle. Fresh vegetations on aortic wall. Chronic passive congestion of lungs and all abdominal viscera.

COMMENT

Bland, White, and Garland¹ have recently reviewed the cases of congenital anomalies of the coronary arteries. They grouped them into two main headings, (a) abnormalities of origin and (b) variations in number, size, and distribution. The latter group, to which the present case belongs, is of less importance clinically, since certain types are not incompatible with long life. It is quite possible that this patient would have survived for many years had he not had the additional disabling factor of acquired rheumatic valvular disease.

The first representations of the coronary arteries in the embryo are endothelial cushions, which become columns and grow out into the superficial portion of the myocardium. These columns then become hollow. It takes but little imagination to conceive of a part of a primary cushion becoming separated from the main portion and developing into an independent artery alongside of the parent. Whatever factors cause this separation may be effective also in guiding the growing artery into abnormal pathways, so that the distribution is unusual as well as manner of origin. In this case, the vessels apparently were of sufficient size to convey enough blood to the right ventricle, but the orifices were small, together being distinctly less than the normal. This functional stenosis leading to inadequate blood supply to the right ventricle was no doubt the cause of its thin wall.

SUMMARY

A case is reported of a congenital doubling of the right coronary artery, with stenosis of the orifices, associated with rheumatic aortic valvular disease, angina pectoris, and enlargement.

Thanks are due to Dr. R. E. Semmes, who performed the alcohol injections and the nerve root sections; Dr. N. E. Leake, who performed the autopsy with me; Dr. John Maury, Jr., and Dr. William C. Colbert, who permitted me to study this patient while on their services.

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Department of Reviews and Abstracts

Selected Abstracts

Code, Charles F., Dingle, W. T., and Moorehouse, V. H. K.: The Cardiovascular Carotid Sinus Reflex. *Am. J. Physiol.* 115: 249, 1936.

A study has been made of the anatomy of the carotid sinus region of the dog in order to determine the nerves ending in the carotid sinus. The physiological function of the nerves supplying the sinus has been investigated and the following results obtained.

Anatomically, it has been found that the carotid sinus possesses three sources of nerve supply: a branch from the posterior division of the glossopharyngeal nerve, a branch from the superior cervical ganglion, and a small nerve which accompanies the internal carotid artery.

Electric stimulation indicates that the nerve accompanying the internal carotid artery is not concerned in the carotid sinus reflex.

A study of the comparative responses of the sympathetic nerve and the sinus nerve to electric stimulation clearly indicates the greater importance of the sinus nerve.

On the basis of acute and survival denervation experiments it is concluded that the cardiovascular components of the sinus reflex are conducted solely through the sinus nerve.

Evulsion of the sinus nerve is submitted as a method of carotid sinus denervation, and the surgical approach to the sinus nerve is described.

These experiments lend support to the view that the carotid sinus operates entirely through a depressor mechanism.

AUTHOR.

Krass, Ernst: The Effect of Electric Current on Intravascular Clots in Animal Experiments. *Arch. f. klin. Chir.* 184: 383, 1936.

The effect of passing an electric current through experimentally produced intravascular clots was studied to determine whether fixation of the clot to the vessel wall could be attained as a step toward the prevention of embolism. The clots were produced by injecting sodium morrhuate solution into the jugular veins of dogs. Direct current of varying intensity and for different periods was passed through the occluded segment of the vessel. In that portion of the vein which was directly in contact with the cathode, the clot became retracted, softened, and firmly attached to the intima. No such changes occurred at the anode. Similar results were obtained if the cathode was placed on the skin overlying the occluded vein. Rapid organization of the clots followed with restoration of the vascular lumen.

L. M. Z.

Doering, B.: Experimental Production of Hypertrophy of the Left Heart in Rabbits by Ephedrine and Ephetonin. *Beitr. z. path. Anat. u. z. allg. Path.* 96: 309, 1936.

Fourteen rabbits were injected subcutaneously with ephedrine or ephetonin daily for 44 to 154 days except for irregularly interposed rest periods of a day to avoid

immunization. The dose was 0.05 gr. per day. As a result, the blood pressure increased markedly in the first period of the experiment, but decreased slowly after about 100 days to the normal and could not be raised again with repeated injections. Rabbits killed during the high pressure period generally showed a distinct hypertrophy of the left and a slight hypertrophy of the right ventricle. Four animals were killed a long time after the high pressure period was over. No hypertrophy of the ventricles was found in these rabbits.

The author believes he has proved the possibility of the return of the hypertrophic heart to a normal size after eliminating the cause for the hypertrophy.

A. V.

Plá, Juan Carlos and Fabregat, Agosto: Syndrome Characterized by Simultaneous Crisis of Tetany and Paroxysmal Tachycardia. *Rev. argent. de cardiol.* 2: 265, 1935.

A case is reported of a woman affected by parathyroid insufficiency who showed simultaneous attacks of tetany and paroxysmal tachycardia. The progress of the patient and the success obtained with an adequate treatment warrant the following statements:

a. Paroxysmal tachycardia may be a clinical manifestation of parathyroid insufficiency.

b. There can be a coexistence of paroxysmal tachycardia and tetany.

c. Parathormone may in these cases (as in this one) cure the paroxysmal tachycardia.

H. McC.

Finkelstein, Leonard E.: Cardiomegalia Glycogenica Circumscripta. *Am. J. Med. Sc.* 191: 415, 1936.

A case of idiopathic hypertrophy of the heart, reported in 1924 by Carrington and Krumbhaar, is reviewed. Histologically the myocardium showed many areas of apparent vacuolization similar to those found in the cardiac type of von Gierke's disease. Moreover, the presence of glycogen can be demonstrated in this specimen.

Such localized deposits of glycogen in an otherwise unexplained hypertrophy of the heart may represent a localized form of von Gierke's glycogen storage disease, or a healing stage of that disease, or merely a cause of idiopathic hypertrophy.

The descriptive term "cardiomegalia glycogenica circumscripta" is suggested for this condition.

AUTHOR.

Coronini, C., Popper, H., Neugebauer, R., and Piringer, W.: Postmortem Blood and Organ Cultures of Acid-Alcohol Fast Bacilli in "Rheumatic" Heart Disease. *Virchows Arch. f. path. Anat.* 296: 422, 1936.

Cultures of the blood and organs were made of 161 persons who died of rheumatic heart disease. A total of 588 organ cultures and 166 blood cultures were made.

It was found that the more acute the rheumatic heart disease was, the higher was the percentage of tubercle bacilli found in cultures: in 18 cases of acute and subacute rheumatic endocarditis, 10 were positive; in 15 cases of chronic recurrent endocarditis, 7 were positive; in 45 cases of valvular insufficiency with superimposed acute verrucous endocarditis, 15 were positive; in 57 cases of old endocarditis without recent changes, only 7 were positive. Even cases of subacute ulcerative endocarditis showed positive cultures.

In most cases the bacilli so obtained caused typical tuberculosis when injected into guinea pigs.

The highest percentage of positive cultures was obtained from the tonsils and the myocardium. Less often positive cultures were obtained from the spleen and the blood, and in two cases positive cultures were obtained from the endocardium.

The authors conclude that the tubercle bacillemia found in these cases is a secondary invasion of the bacilli into the blood which in hyperallergic subjects manifests itself as rheumatic disease. Cocci, which also were frequently found in the cultures, are regarded by the authors as of secondary importance.

A. V.

Von Rutich, E.: The Duplicated Sound in the Auscultatory Method of the Blood Pressure Determination. *Klin. Wchnschr.* 15: 54, 1936.

In the auscultatory method of blood pressure determination, a duplication of arterial sounds is frequently heard for some time between systolic and diastolic pressures. This duplicated sound can be detected over the eubital or popliteal arteries of both normal and sick subjects. It is inconstant and bears no relationship to any specific pathological process. The author suggests that this phenomenon is produced by the contour of the pulse wave. The two phases of the arterial wave stretch the arterial wall at the lower edge of the cuff twice in quick succession and set up the vibrations.

R. K.

Arnott, W. M., and Kellar, R. J.: The Effect of Renal Denervation on the Blood Pressure in Experimental Renal Hypertension. *J. Path. & Bact.* 42: 141, 1936.

Bilateral nephrectomy did not lead to hypertension in the rabbits which survived the operation; on the contrary, a progressive fall was observed. Sodium oxalate nephritis had been found previously to cause hypertension in animals; it failed to alter the blood pressure curves in bilaterally nephrectomized animals, causing the authors to conclude that its effect is due to renal damage.

Denervation of the kidney abolishes the hypertension of oxalate nephritis in animals in which one kidney remains intact.

L. H. H.

Sansum, W. D.: The Favorable Influence of Adequate (Higher) Carbohydrate Diets on the Blood Pressure of Diabetic Patients. *South. Med. J.* 29: 414, 1936.

In addition to the beneficial effect of the high carbohydrate diet on the incidence of ketosis, and on the state of nutrition with minimal insulin dosage, Sansum here states that "the incidence of premature arteriosclerosis is being prevented in children." The factor implicated in the older diabetic diets seems not to be the acid-base balance, but the high cholesterol content. The author writes of the effects on arteriosclerosis; the reader must presume that hypertension, indicated in the title, always accompanies the arteriosclerosis.

L. H. H.

Hines, E. A., Jr., and Brown, George E.: Arteriolar Hypertonus Without High Blood Pressure (Latent Hypertension). *Proc. Staff Meet., Mayo Clin.* 11: 21, 1932.

The authors have observed middle-aged and elderly patients who had a hypertension type of sclerosis affecting the arterioles but who did not have hypertension. Fifty such patients were subjected to a special study of their blood pressure reactions. Each patient was subjected to a cold pressor test, and on ten patients hourly readings of blood pressure were carried out. All of the subjects gave a

definite hypertensive type of reaction to the cold pressor test. The mean reaction in blood pressure for the group was 38.4 mm. of mercury, systolic, and 26.4 mm., diastolic. In 70 per cent of the cases the return to the previous basal level was prolonged abnormally. The hourly reading of blood pressure revealed marked lability in each of the ten cases studied in this manner. The lability was in the lower ranges as compared to the lability in the higher ranges of subjects with essential hypertension. There was a family history of hypertensive cardiovascular disease in 82 per cent of the cases.

These studies suggest that such patients have a latent or subclinical form of hypertension. They display an abnormality of the blood pressure, manifested by momentary hypertension and excessive responses to stimulation. This hyperreaction of the blood pressure is indicative of an arteriolar hyperactivity. The authors believe that the arteriolar hyperactivity is the mechanical factor producing the changes in the arterioles. The appearance of these manifestations may precede the clinical stages of essential hypertension.

AUTHOR.

Allen, Edgar V.: How Arteries Compensate for Occlusion: An Arteriographic Study of Collateral Circulation. *Arch. Int. Med.* 57: 601, 1936.

The arteriograms show evidence of profuse collateral circulation in cases of occlusive arterial disease. Logical and purposeful design in the development of collateral circulation is apparent. By methods which have been designated as anastomosis, lateral projection, prolongation, terminal branching, and network formation, a collateral circulation develops which can compensate for extensive occlusion of the chief arteries of an extremity. There is indirect but entirely logical and convincing evidence that collateral arteries are chiefly arteries which are present normally but which have increased in size as a response to a demand for increased function which arises as a result of occlusion of the main arteries.

AUTHOR.

Wilson, Harwell, Roome, Norman W., and Grimson, Keith: Complete Sympathectomy: Observations of Certain Vascular Reactions During and After Complete Exclusion of the Sympathetic Nervous System in Dogs: an Experimental Study. *Ann. Surg.* 103: 498, 1936.

Observations upon the blood pressure of normal dogs during the three stages of complete sympathetic exclusion showed that the blood pressures tend to recover after each stage of sympathectomy; however, there was no evidence of marked overcompensation; that is, there was no significant rise of blood pressure above the normal. After the right thoracic chain was removed, half the animals maintained a blood pressure very slightly above normal, and one-half fell below, but all were within the normal range. Following removal of the left thoracic chain with section of the greater splanchnic nerve, the greatest and most continued depression occurred. Abdominal sympathectomy usually produced no significant change in the blood pressure. Six of the animals upon which complete sympathetic exclusion had been performed were kept for periods of many months, and all have shown blood pressure recovery that casts doubt on the idea of maintained hypotension following any type of sympathetic surgery. The animals studied, however, were normal, while surgical procedures which have been described by various authors are directed toward lowering an abnormally high arterial tension. The depression of the blood pressure which follows section of the cervical spinal cord, and high spinal anesthesia in normal dogs, was absent in recently completely sympathectomized animals. This finding agrees with the commonly accepted idea that the depressor effect of these two procedures is due to the removal of tonic vasoconstrictor impulses passing

down the cord from the vasomotor center and leaving it by the thoracolumbar outflow. The transient rise of the blood pressure which may occur at the moment of section of the spinal cord of normal dogs was also absent in the sympathectomized animals. Both these observations suggest that in recently sympathectomized animals there is no important vasoconstrictor outflow from the spinal cord below the first dorsal segment and that in the intact animal all such outflow is carried through the sympathetic chains.

Comparison of the blood pressure maintained shortly after sympathectomy with the blood pressures resulting immediately from high spinal anesthesia and cervical cord section in normal dogs indicates the presence in the former condition of some factor maintaining the blood pressure at a higher level than in the latter conditions, although in all there is presumably nearly complete loss of vasomotor tone. Sympathectomized animals with lowered blood pressures had bleeding volumes which were approximately normal, which suggests that such animals should withstand hemorrhage, trauma, or an operation approximately as well as normal dogs.

The blood pressure after complete sympathectomy remains at a higher level than would be expected after withdrawal of all vasoconstrictor tone. The possibility of a peripheral vasoconstrictor mechanism is suggested.

E. A.

Nagy, Michael: Operatively Healed Case of a Symptomatic Raynaud's Disease Caused by a Cervical Rib. *Monatschr. f. Psychiat. u. Neurol.* 91: 300, 1935.

The right hand of a farmer, fifty-six years old, was cold and painful. The typical spastic attacks were absent. The finger tips were cyanotic. The radial pulse was absent. X-ray examination showed a cervical rib 8 cm. long. After resection of the cervical rib most of the vascular disturbances disappeared. It would seem that in this case they were caused by the pressure of the cervical rib on the brachial nerve plexus.

J. K.

Bierman, W.: The Temperature of the Skin Surface. *J. A. M. A.* 106: 1158, 1936.

A detailed report is made of the results of skin temperature readings of all parts of the body under varying conditions of health and disease, both from personal observation and from many sources in the literature.

Aside from the obvious usefulness of such readings in peripheral vascular disease (separating spastic from organic occlusion), their value in other disease conditions, and in estimating the influence of drugs and physical measures, is considered.

L. H. H.

Alcock, P., Berry, J. L., and Daly, De Burgh: The Action of Drugs on the Pulmonary Circulation. *Quart. J. Exper. Physiol.* 25: 369, 1935.

Studies were made on the isolated lung preparations of the dog under negative pressure ventilation and perfused with defibrinated blood. Acetylcholine in the smallest effective doses causes a slight fall in pulmonary arterial pressure, and in large doses a rise in pulmonary arterial pressure. The effects are in part, if not solely, independent of bronchomotor mechanisms. The pulmonary arterial pressure rise or fall due to acetylcholine injections occur in nicotine preparations, are enhanced by eserine and suppressed by atropine. Adrenalin in small doses may have no effect upon the pulmonary arterial pressure and yet cause an increase in venous outflow. A method is described for measuring the blood inflow and outflow from lungs under negative pressure ventilation.

E. A.

Meyer, Fritz: The Causes of Oxygen Deficiency in the Tissues of Patients with Circulatory Diseases. *Klin. Wehnsehr.* 15: 48, 1936.

An insufficient supply of oxygen in the tissues in circulatory diseases may be due to three different causes: (1) an insufficient oxygenation of the arterial blood (detected by blood gas analysis), (2) a sluggish capillary circulation, and (3) a decreased permeability of the wall of the capillaries to oxygen.

The differential diagnosis between the latter two can be made by determinations of the CO_2 and O_2 tensions in the tissue, following a method described previously by the author. When capillary circulation is slowed, the O_2 tension in the tissue is diminished, and the CO_2 tension is increased. The difference between the gas tensions of the tissues and of the capillaries is not changed. A disturbance of the permeability of the capillaries produces a different picture. The O_2 tension in the capillaries remains normal, but decreases in the tissues. The CO_2 tension in the tissue is only slightly increased. The differences in the tensions between the tissues and the capillaries are markedly increased for O_2 and slightly for CO_2 . The results are summarized by means of a special nomogram. Only two of the fourteen patients with circulatory diseases had a decreased permeability of the capillaries to oxygen.

R. K.

Gauer, Otto: The Velocity of Pulse Wave in the Aorta and Femoral Artery of Human Beings. *Ztschr. f. Kreislaufforsch.* 28: 7, 1936.

Measurement of the velocity of pulse wave in the aorta and femoral artery in a healthy person twenty-four years of age was determined with the following results: In the thoracic aorta in a standing or reclining position the rate was 3.8 to 4 meters per second. It increased in the abdominal aorta to 4 to 4.5 meters per second. In the femoral artery, in a standing position, the rate was 12 to 13 meters per second, and in a reclined position 8.5 meters per second. Control examinations on other individuals showed only a slight variation from these findings.

J. K.

Gartner, Wilhelm: The Clinical Picture and Circulatory Disturbances in Paraganglioma of the Adrenals. *Ztschr. f. Kreislaufforsch.* 28: 82, 1936.

The author assembles and critically analyzes twenty-two cases from the literature. He finds that the tumor is unilateral, usually on the right side, and that it rarely metastasizes. All patients have paroxysmal hypertension with the pressure going up as high as 300 systolic; these attacks, as time goes on, increase in frequency and intensity. There are usually several attacks a day; the patient between attacks appears to be normal. The patients have hemorrhages, especially from the nose or into the retina with consequent visual disturbances. They complain of pain over the entire body, especially in the back over the adrenals. Glycosuria occurs only during an attack. Chronic hypertension may eventually appear, or the pressure between attacks may remain normal. Apoplexy may occur during an attack, manifesting itself by unconsciousness, motor unrest, epileptiform movements, or visual disturbances. Such an event may lead to the mistaken diagnosis of glomerulonephritis. The patient may recover from the apoplectic seizure, but a succeeding one may cause death. In several patients death was preceded by coma. Treatment consists in removing the tumor, and in several instances this procedure was followed by complete cure.

L. N. K.

Goldsmith, Grace A.: The Effectiveness of Acetyl- β -Methylcholine Given by Mouth as a Vasodilating Agent. *Ann. Int. Med.* 9: 1196, 1936.

Acetyl- β -methylcholine administered orally to 29 patients in doses of 50 to 1,500 mg. caused an average maximal rise in the temperature of the skin of the digits of 5.82° C. Vasodilation failed to occur in only one case in which an adequate dose was given. The vasodilating effect varies tremendously with different patients, in different pathological conditions, and in the different digits of a given individual. The vasodilation is slow in onset and is of relatively long duration. An adequate dose seems to be between 1,000 and 1,500 mg. No significant changes were produced in blood pressure or pulse rate in the cases studied.

E. A.

Clark, Richard J., Means, James H., and Sprague, Howard B.: Total Thyroidectomy for Heart Disease. *New England J. Med.* 214: 277, 1936.

This is a report of the results of total ablation of the thyroid gland in twenty-one cardiac patients operated on at the Massachusetts General Hospital between July, 1933, and May, 1935. Nineteen patients had congestive failure and two had angina pectoris. Conclusions are, therefore, based almost wholly on an experience with congestive failure.

Fifteen patients are now dead. In about one-fourth of the entire series the operation was considered worth while; in three-fourths it was not.

The relatively poor results in the series depended to a considerable degree upon the difficulty in selection of cases and in the fact that too severe cases were originally chosen. The contraindications to operation are numerous, but in cases well selected and handled, worthwhile results were secured, at least temporarily, in 50 per cent.

There is a small group of patients with cardiac failure in whom medical therapy is ineffective in controlling the progressive loss of cardiac reserve for whom total thyroidectomy offers an even chance or worthwhile improvement.

Avoidance of the grosser manifestations of myxedema has not been found difficult. Small daily rations of thyroid usually accomplish this purpose. In some cases, however, at a metabolic level above that of complete myxedema, low rate symptoms have been troublesome.

It is believed that the procedure must be further studied before its usefulness in the treatment of heart disease can be fairly evaluated.

AUTHOR.

Feinberg, Sydney C.: The Treatment of Coronary Artery Disease by Intravenous Injections of Hypertonic Saline Solution. *Am. J. M. Sc.* 191: 410, 1936.

Six patients with severe and intractable angina pectoris due to coronary artery disease who were seriously incapacitated and had not improved on rest and customary therapy were treated with repeated intravenous injections of hypertonic saline solution over long periods of time.

Definite and continuous improvement has been noted in their clinical condition.

The hypothesis is presented that the clinical improvement may be due to the fact that the treatment encourages a more rapid development of collateral circulation in the heart wall.

AUTHOR.

Book Reviews

L'ARTERIOGRAPHE DES MEMBRES ET DE L'AORTE ABDOMINALE. By Henri Reboul. Paris, 1935, Masson & Cie. 136 pages, 82 illustrations.

The first half of this monograph on arteriography of the extremities and the aorta is devoted to a survey of the problem, with an historical review and discussions of the use of lipiodol, sodium iodide, uroselectan, l'abrodyl, tenebryl, thorotrast, and collothor. The advantages and disadvantages of each are weighed. The author, apparently, confined his efforts, for the most part, to tenebryl and thorotrast. He considers carefully the fate of thorotrast in the reticulo-endothelium system, and, although this has been a matter of considerable debate in this country, he does not, apparently, feel that it is of sufficient gravity to discourage the use of this substance. Tenebryl (diiodomethane sulphonate of sodium), a substance little used in this country, has been used extensively by Reboul in his cases. He stresses the pressure under which the substance is injected as being of great importance. This point has not been emphasized much in the United States. Pressures of 1,100 to 1,800 gm. are used.

In a chapter on incidents and accidents with arteriography, he reports those of which he has knowledge. They are, for the most part, minor. A few instances of gangrene of the limb are included, but, as most of these cases are potentially gangrenous, one wonders how much the arteriography had to do with the production of gangrene. Dos Santos is quoted as reporting 1,500 injections with only one serious accident, which required ligation of the femoral artery. Recovery followed without gangrene.

The second half of this work consists mainly of plates of arteriographic studies, which are among the finest the reviewer has ever seen. These are accompanied by short case histories, and the following conditions are portrayed: normal arteries, syphilitic arteritis, presenile arteritis, senile arteritis, diabetic arteritis, infectious arteritis, juvenile arteritis (Buerger), Raynaud's disease, Volkmann's syndrome, arterial spasm, aneurisms of various arteries, osteosarcoma, abscesses and tumors of the extremities, and Paget's disease. In addition, there are plates showing arteriographic studies of the aorta in a number of conditions.

One may quarrel with the classification of peripheral vascular disease used by Reboul, but there is no question regarding the value of this monograph to all workers interested in arteriography.

I. S. W.

THE PHYSIOLOGY OF THE CIRCULATION DURING PUBERTY. By Gustav Nylin. Acta Medica Scandinavica, Supplementum LXIX, Stockholm, 1935, 51 pages, with diagrams and figures.

This reprint, in German, gives the results of investigations on the various utterances of puberty in girls. Observations on the general development of the body, the changes in the exterior, the variations in standard metabolism, and blood flow and vital capacity were made. Twelve children who were living at the State Institution for the Blind in Stockholm were chosen as far as possible in the stage of development where there was reason to expect that the onset of puberty was imminent.

The reports are divided into three sections: first, growth during puberty; second, standard metabolism; and third, the circulation and vital capacity. Individual diagrams and photographs are included for each subject. The observations were continued over a period of years.

A summary of results relating to the circulation shows that the arteriovenous oxygen difference under standard conditions was remarkably constant during growth; from which it follows that the blood flow is a direct function of standard metabolism. Thus, the minute volume of the heart during the puberty maximum in height growth, like the standard metabolism, was increased somewhat above that corresponding to growth in height and weight.

The pulse rate decreased successively during the whole development and showed no signs of increasing with the onset of puberty.

The gains in stroke volume and heart volume were parallel, and during the puberty maximum exhibited a rapid increase, corresponding to the increase in body surface. The relation between heart volume and stroke volume was constant during development.

The painstaking care with which the observations were made and the duration of time over which they extended should make this a useful contribution to the study of the phenomenon of growth during this period of life. The number of cases is small, however.

Jl. McC.

LEÇONS DE CARDIOLOGIE faites à l'hôpital Broussais. By Professor Ch. Laubry with the collaboration of Drs. V. Aitoff, Jean Cottet, Ed. Doumer, R. Heim de Balzac, A. Jaubert, J. Lemant, J. Louvel, Georges Marchal, M. Pommairoux, D. Routier, L. Samain, Ad. Van Bogaert, and J. Walser. (Première série.) G. Doin & Cie., Paris, 1936, 245 pages with 79 illustrations.

Professor Laubry and his associates have organized a course in cardiology which consists of three series of lectures given in rotation in successive years, each lecture being given by a member of the staff who has particular interest in the subject under consideration. In this volume we have the lectures given in one year, that is one third of the total "Cours de perfectionnement sur les maladies du cœur et des vaisseaux." The first nine lectures (136 pages) take up the various arrhythmias; the remaining seven lectures deal with water balance, radiology, cyanosis, hematological disturbances in relation to heart disease, recent ideas concerning pathological disturbances of the veins, the bacteriology of endocarditis and rheumatic fever, and the use of sedative medication in heart disease. The lectures are clearly given and well illustrated; the reader should consider them as lectures and should not expect to find references or an index. This volume of lessons is not intended to serve as a complete textbook but should be of interest especially to those who would like to study under well-known French teachers and to those who are interested in teaching.

E. H.

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